Neurology

OFFICIAL JOURNAL OF
THE AMERICAN ACADEMY OF NEUROLOGY

OCTOBER--1959
Volume 9 - Number 10

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TINY TABLET UNDER TONGUE
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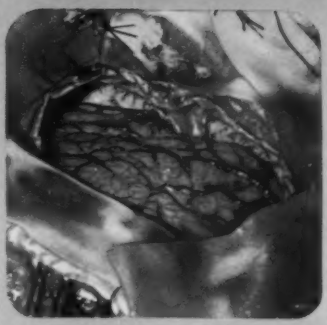

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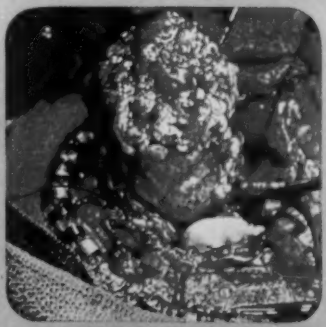

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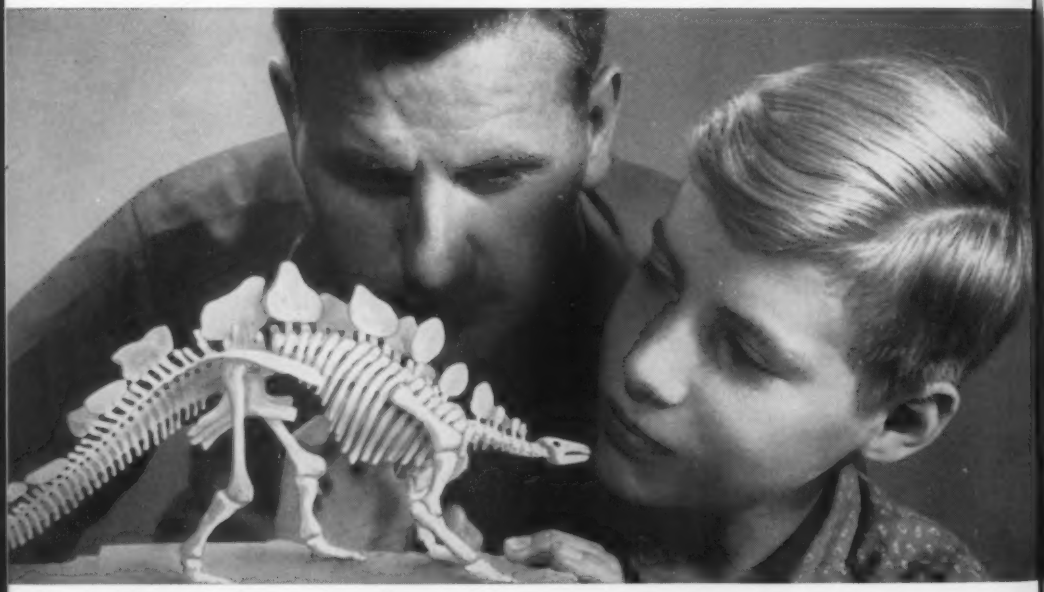

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NEUROLOGY, the official publication of the American Academy of Neurology, has been instituted to provide a medium for prompt publication of articles dealing with neurology and its cognate fields and to stimulate individual investigation in these various fields.

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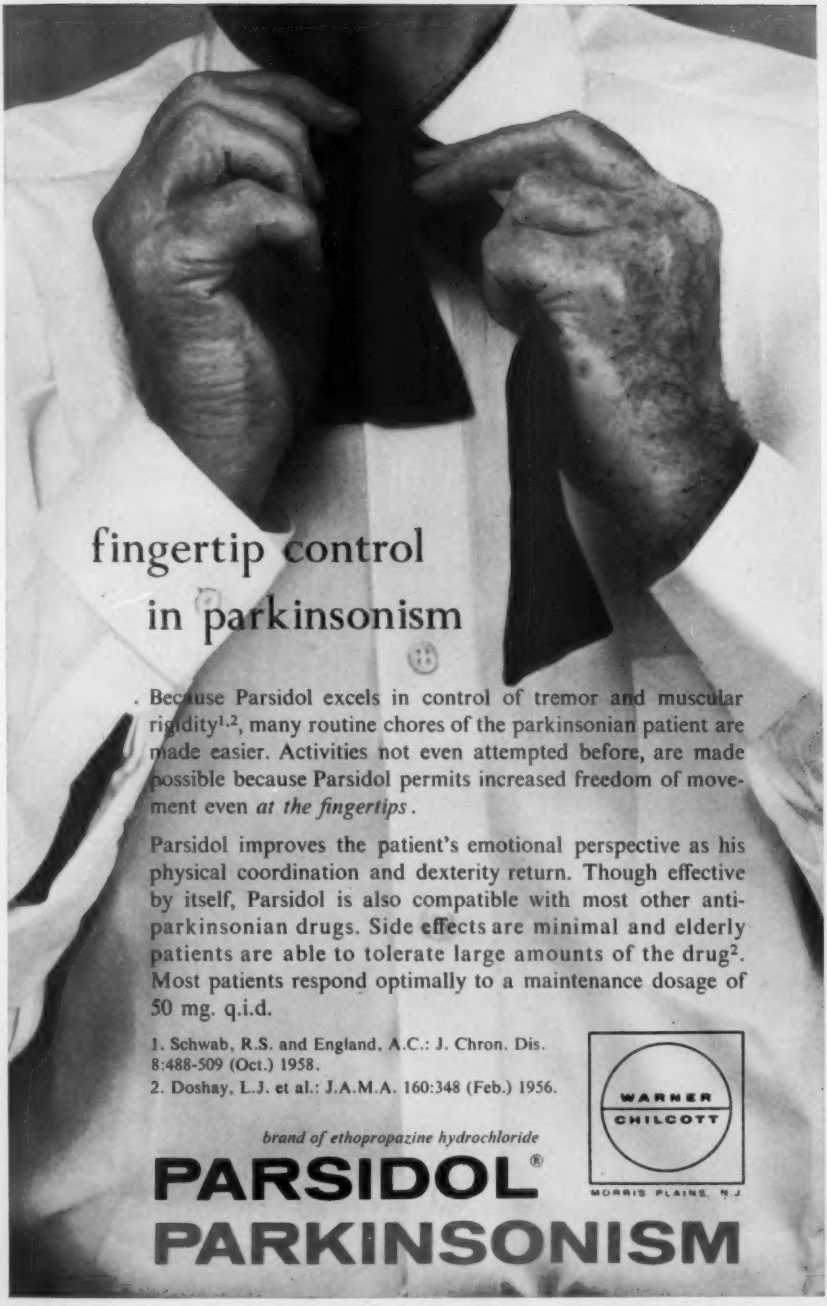
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1. Schwab, R.S. and England, A.C.: J. Chron. Dis. 8:488-509 (Oct.) 1958.
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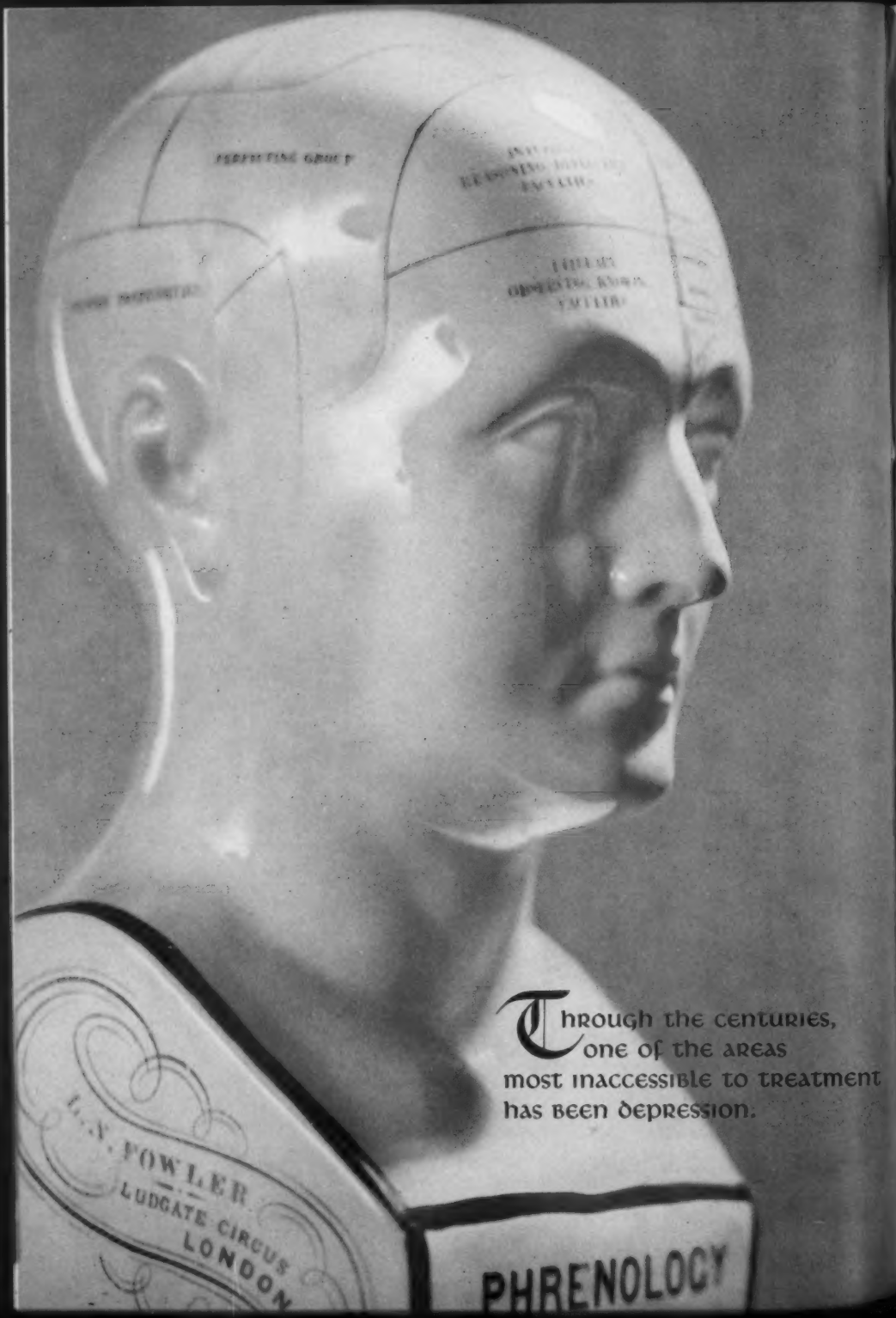

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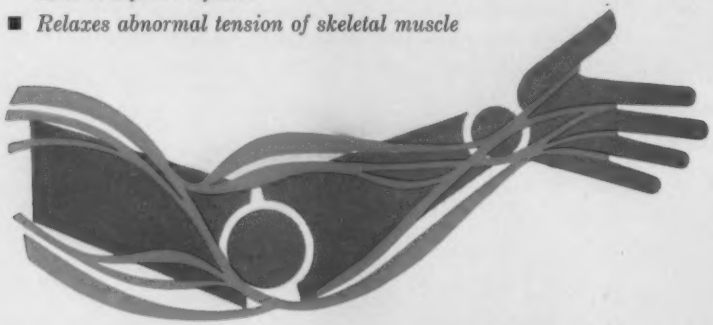

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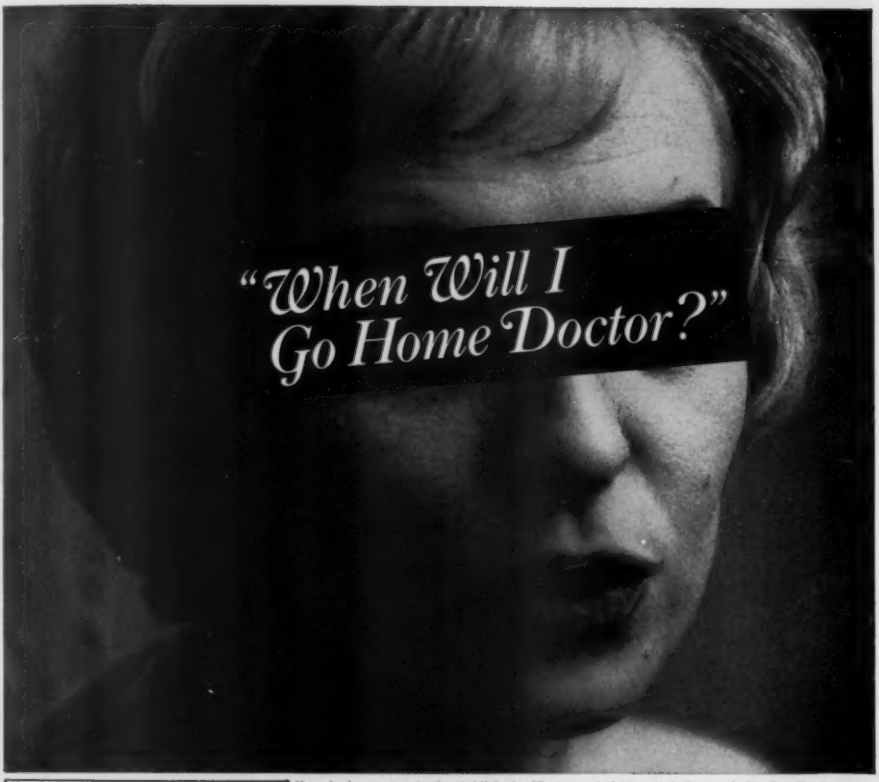

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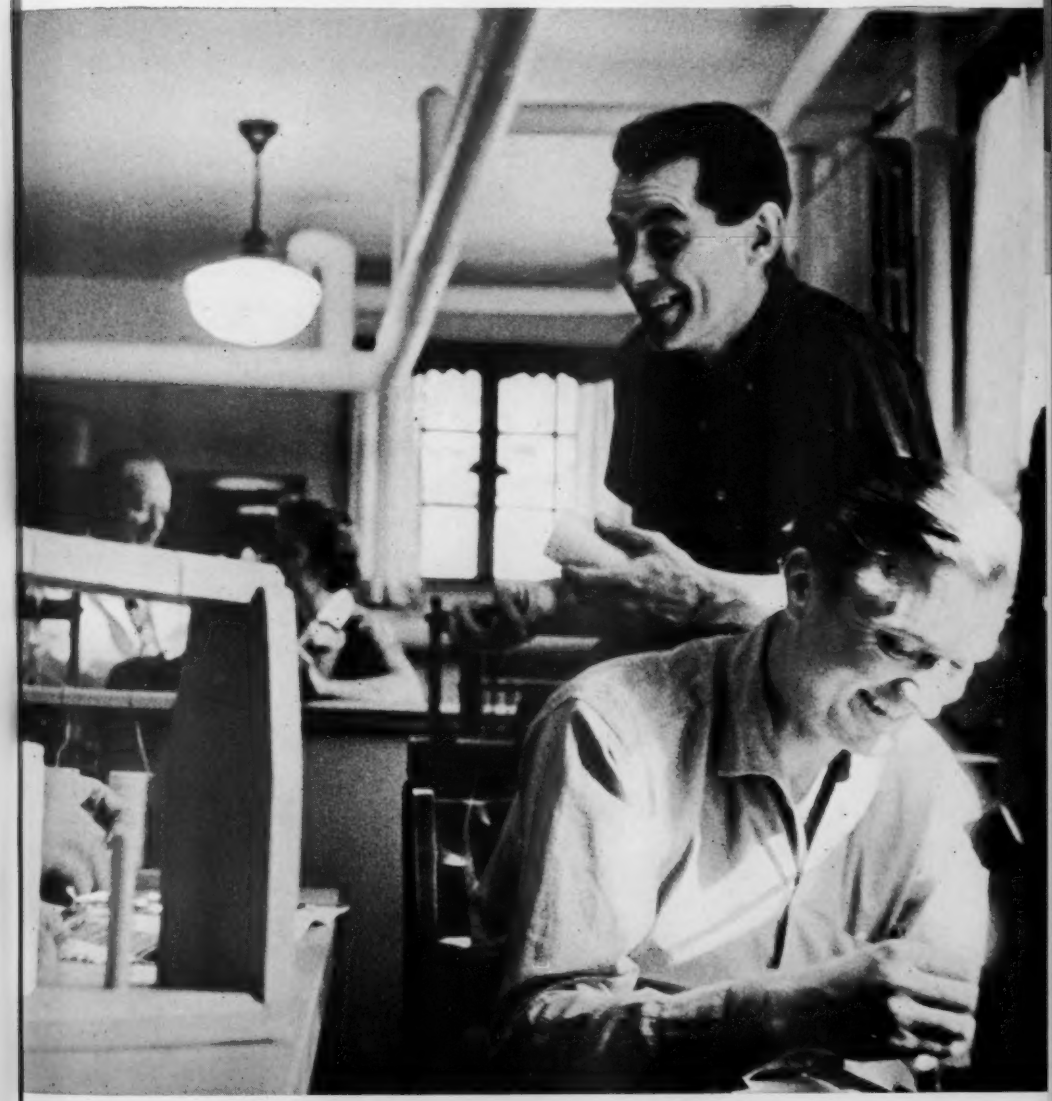

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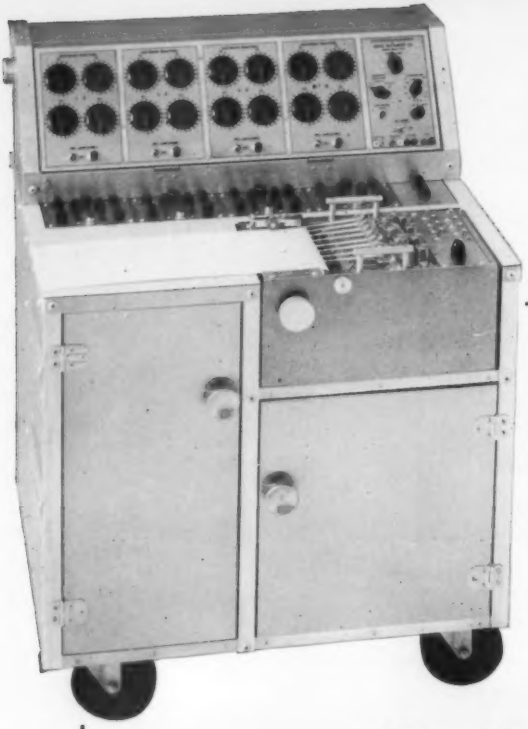

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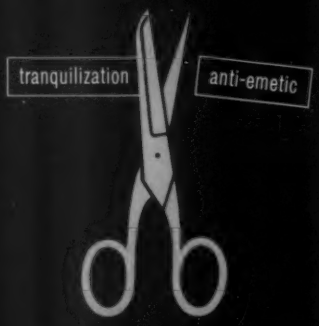

Virtual freedom of Mellaril from major toxic effects is due to greater specificity of tranquilizing action, divorced from such "diffuse" effects as anti-emetic action.

MELLARIL is virtually free of such toxic effects as

- jaundice
- Parkinsonism
- blood dyscrasia

"Thioridazine [MELLARIL] is as effective as the best available phenothiazine, but with appreciably less toxic effects than those demonstrated with other phenothiazines. . . . This drug appears to represent a major addition to the safe and effective treatment of a wide range of psychological disturbances seen daily in the clinics or by the general practitioner."

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"POVERTY" OF SIDE EFFECTS

"The most striking aspect of thioridazine [Mellaril] therapy is the poverty of side effects.... In its lack of side effects and low toxicity, it is superior to all other tranquilizing drugs tested. For this reason also it is well tolerated by patients, particularly those who are not hospitalized and who frequently discontinue their medication because of dizziness, sleepiness, increased tension or parkinsonism with other drugs."[2]

NEGLIGIBLE SIDE EFFECTS

"Side effects were negligible at all dosage levels: no incidence of parkinsonism or other extrapyramidal symptoms. Minimal sedation, on the whole lower than with other tranquilizing agents. No alteration in liver function, urine or blood. No photosensitivity. Patient acceptability was exceptional: lack of drowsiness, lethargy or 'washed out' feeling, permitted patients to carry on normal everyday activities. Orthostatic hypotension was absent. The initial 'keyed up' tense feeling common to other drugs of this type was absent.... Patients forced to interrupt treatment with other phenothiazine derivatives because of parkinsonism or other extrapyramidal symptoms were able to continue therapy with thioridazine without appearance of parkinsonism."[3]

SINGULARLY FREE OF SIDE EFFECTS

"The extrapyramidal syndrome was not encountered in any of its forms. Dizziness and sleepiness responded to a reduction in dosage. Other side effects did not occur.... It is singularly free from the side effects ordinarily seen with these [phenothiazine] compounds."[4]

ABSENCE OF SIGNIFICANT SIDE EFFECTS

"None of the following toxic effects, so common after administration of the phenothiazines, was present during the period of Thioridazine administration: Parkinsonism or Parkinson-like symptoms, photosensitivity, orthostatic hypotension, bone-marrow depression."[1]

MINIMAL SIDE EFFECTS

"Side effects such as extrapyramidal activity, jaundice and photosensitivity have not been observed in patients treated with Thioridazine [Mellaril]. Extrapyramidal side effects produced by other phenothiazines have disappeared promptly with no deterioration in the behavioral response when these patients have been shifted to Thioridazine."[5]

NO JAUNDICE

"No allergic reactions were observed such as skin eruptions, jaundice or agranulocytosis. Central nervous system toxicity, as manifested by extrapyramidal effects, seizures, and excitement did not occur despite the use of high doses (up to 2000 mg.) of the drug."[6]

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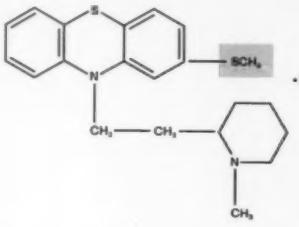
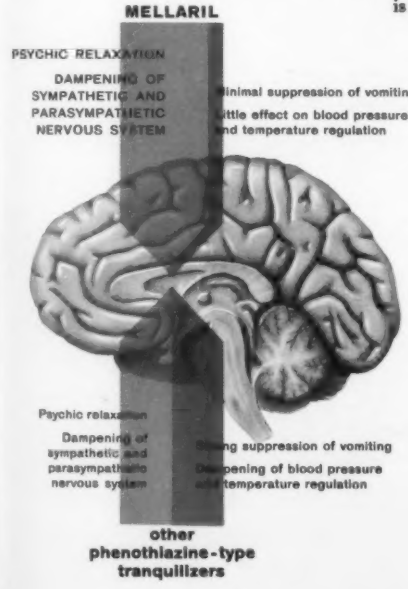
tranquilization | anti-emetic

a new advance in tranquilization:
greater specificity of tranquilizing action plus fewer side effects



Of 109 phenothiazines synthesized by Sandoz, Mellaril was selected as the most promising on the basis of extensive evaluation. The presence of a thiomethyl radical ($S\text{-}CH_3$) in the position conventionally occupied by a halogen in other phenothiazines is unique and could be responsible for the relative absence of side effects and greater specificity of psychotherapeutic action. This is shown clinically by:

1 **A specificity of action on certain brain sites in contrast to the more generalized or "diffuse" action of other phenothiazines. This is evidenced by a lack of appreciable anti-emetic effect.**



2 **Less "spill-over" action to other brain areas – hence, absence of undue sedation, drowsiness or autonomic nervous system disturbances.**

3 **A notable absence of extrapyramidal stimulation.**

4 **Lack of impairment of patient's normal drive and energy, while achieving psychomotor control in mental and emotional disorders.**

5 **Virtual freedom from toxic effects – jaundice, photosensitivity, skin eruptions, disturbed body temperature regulation, blood forming disorders have been absent in reports currently available.**

These properties add up to a greater margin of safety in general office practice, in ambulatory psychiatric out-patient clinics, and in hospitalized patients.

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specific, effective tranquilizer • safer at all dosage levels

excellent clinical response

In office practice and in hospitalized patients, Mellaril has proved highly useful for a wide variety of major and minor emotional disorders (such as anxiety, tension, apprehension, alcoholism, agitated psychoneurosis, agitated psychotic states, etc.).

EXTREMELY SATISFACTORY "... produced extremely satisfactory results in the broad therapeutic range represented in this series."[2]

POTENT AGENT "... appears to be a potent agent in the symptomatic management of a variety of psychiatric states."[4]

MAJOR ADDITION TO THERAPEUTICS "This drug appears to represent a major addition to the safe and effective treatment of a wide range of psychological disturbances seen daily in the clinics or by the general practitioner."[1]

AN ACTIVE AGENT "Thioridazine is an active therapeutic agent. ... It is effective in a variety of psychiatric disorders, including schizophrenic reactions. ... The drug is particularly advantageous for a group of schizophrenic patients who are sometimes made worse by other phenothiazine derivatives or Rauwolfia alkaloids. It should also be suitable for treating patients with psychoneuroses and chronic brain syndrome."[6]

EVEN IN VERY SEVERE CASES "Of the 152 patients treated 25 have been released and they have not suffered a relapse. This proportion is significant if we stop to consider that we are dealing only with acute cases which had been considered hopeless and obviously destined to finish their days in an asylum."[7]

EXCELLENT THERAPEUTIC RESPONSE "Patients with emotional tensions resulting from the stress and strain of life ... were treated with Mellaril at the dosage level of 10 mg. three times daily. In 94 such patients, 83 obtained an excellent therapeutic response."[8]

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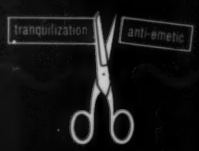

"... extremely satisfactory results ..."
in a clinical spectrum ranging from
minor nervous disorders to
severe psychotic disturbances[3]

RESULTS WITH MELLARIL IN 194 PATIENTS[3]

ACUTE PSYCHOTICS	CHRONIC PSYCHOTICS	NEUROTICS
83% satisfactory effect	68% satisfactory effect	57% satisfactory effect
Some cases had complete remission of symptoms. Most were able to return home to useful occupations.	Relief of symptoms in cases permitted easier management and a return to a more or less useful life.	Some cases, complete relief of symptoms. Other cases, partial relief of symptoms.

RESULTS WITH MELLARIL IN PATIENTS PREVIOUSLY TREATED WITH OTHER TRANQUILIZERS[3]

DIAGNOSTIC CATEGORY	IMPROVED %	VERY SATISFACTORY %	SATISFACTORY %	UNSATISFACTORY %
SCHIZOPHRENIA				
Acute	89	61	28	11
Chronic paranoid	84.2	31.6	52.6	15.8
Chronic, other	73.9	21.7	52.2	26.1
Residual	57.1	9.5	47.6	42.9
CHRONIC BRAIN SYNDROME	66.6	33.3	33.3	33.3
CHRONIC PSYCHONEUROSIS	62.5	12.5	50	37.5
CHRONIC PSYCHOSOMATIC DISORDERS	75	25	50	25

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specific, effective tranquilizer • safer at all dosage levels

a guide to administration and dosage

Dosage ranges from 10 mg. three or four times a day in milder situations to 25 mg. three or four times a day for more disturbed patients. In ambulatory psychiatric out-patients, dosages of 50 to 100 mg. three or four times a day have been found adequate. For severely disturbed hospitalized psychotics, dosages of 200 to 300 mg. three times a day may be administered.

Dosage must be individualized according to the condition and degree of response. In all cases, the smallest effective dosage should be determined for each patient.

INDICATION	USUAL STARTING DOSE	TOTAL DAILY DOSAGE RANGE
	ADULTS	
Mental and Emotional Disturbances:		
MILD—where anxiety, apprehension and tension are present	10 mg. t.i.d.	20-60 mg.
MODERATE—where agitation exists in psychoneurosis, alcoholism, intractable pain, senility, etc.	25 mg. t.i.d.	50-200 mg.
SEVERE—in agitated psychotic states as schizophrenia, manic depressive, toxic psychoses, etc.:		
Ambulatory	100 mg. t.i.d.	200-400 mg.
Hospitalized	100 mg. t.i.d.	200-800 mg.
	CHILDREN	
BEHAVIOR PROBLEMS IN CHILDREN	10 mg. t.i.d.	20-40 mg.

PRECAUTIONS: Although possessing a unique structure and a selectivity of action which broadens its therapeutic ratio, the physician should be alert to the possibility of untoward reactions in certain susceptible individuals. In particular, he should watch for potential hemopoietic depression, jaundice or orthostatic hypotension. As with other phenothiazines, Mellaril is contraindicated in severely depressed or comatose states from any cause.

SUPPLIED: MELLARIL Tablets, 10 mg., 25 mg., 100 mg. Bottles of 100.

1. Ostfeld, A. M.: Scientific Exhibit, American Academy of General Practice, San Francisco, April 6-9, 1959. 2. Kinross-Wright, V. J.: Lecture, Clinical Meeting, American Medical Association, Minneapolis, Dec. 4, 1958. 3. Kinross-Wright, V. J.: Scientific Exhibit, Clinical Meeting, American Medical Association, Minneapolis, Dec. 2-5, 1958. 4. Cohen, S.: TP-21, a new phenothiazine, Am. J. Psychiat. *115*:358, Oct. 1958. 5. Glueck, B.: Scientific Exhibit, American Psychiatric Association, Philadelphia, April 27-May 1, 1959. 6. Hollister, L. E., and Macdonald, B. F.: Presented at California Medical Association; Section on Psychiatry, San Francisco, Feb. 25, 1959. 7. Remy, M.: Schweiz. med. Wchnschr. *88*:1221, Nov. 29, 1958. 8. Freed, S. C., in discussion on Thioridazine (Mellaril) in Psychiatric Patients, Hollister, L. E., and Macdonald, B. F., presented at California Medical Association; Section on Psychiatry, San Francisco, Feb. 25, 1959.

- controls neurotic and psychotic patients with anxiety, apprehension, nervous tension
- virtual absence of jaundice, parkinsonism, photosensitivity, dermatitis
- minimal sedation and drowsiness
- does not mask organic conditions such as brain tumors, intestinal obstruction, etc., because of lack of anti-emetic action
- increased specificity of action results in greater safety at all dosage levels

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tranquilization | anti-emetic

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METHANESULFONATE (Benztropine Methanesulfonate)

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Dosage: usual daily dose is 1 to 2 mg., with a range of 0.5 to 6 mg. Frequently, a single dose at bedtime is sufficient to control symptoms for 24 hours. In tranquilizer-induced Parkinsonism, the usual dosage is 1 to 2 mg. two or three times a day. When COGENTIN is used to offset the distressing Parkinson-like symptoms caused by tranquilizers, adequate therapy with these drugs may usually be continued. A decrease in dosage is rarely necessary.

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1. Brock, S., Mod.: Bull. New York Acad. Med. *32*:202, 1956.
2. Doshay, L. J.: Parkinsonism and Its Treatment, Philadelphia, J. B. Lippincott, 1954, pp. 87-88.
3. Doshay, L. J., Constable, K., and Zier, A.: Neurology *3*:360, 1953.

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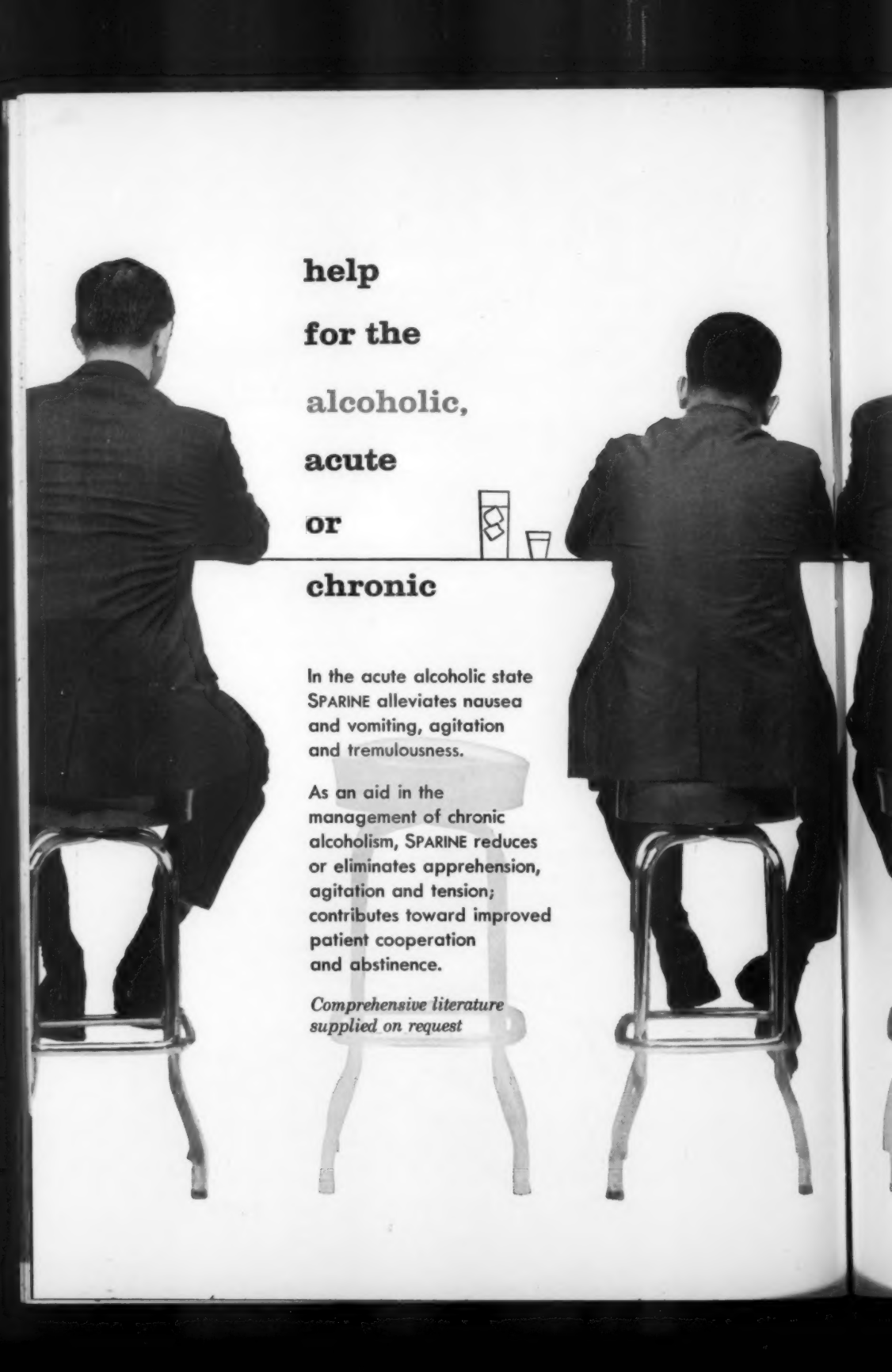
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In the acute alcoholic state SPARINE alleviates nausea and vomiting, agitation and tremulousness.
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ROBAXIN BENEFICIAL IN 92.4% OF SKELETAL MUSCLE SPASM CASES

	NO. PATIENTS	RESPONSE			
		"marked"	moderate	slight	none
Carpenter[1]	33	26	6	1	—
		"pronounced"			
Forsyth[2]	58	37	20	—	1
		"good"			
Lewis[3]	38	25	6	—	7
O'Doherty & Shields[4]	17	"excellent" 14	2	1	0
		"significant"			
Park[5]	30	27	—	2	1
		"gratifying"			
Plumb[6]	60	55	—	—	5
TOTALS	236	184 (78.0%)	34 (14.4%)	4	14

- **Highly potent—and long acting.**[1,2,3]
- **Relatively free of adverse side effects.**[1,2,3,5,6]
- **In ordinary dosage, does not reduce muscle strength or reflex activity.**[1]

REFERENCES: 1. Carpenter, E. B.: Southern M. J. 51:627, 1958. 2. Forsyth, H. F.: J.A.M.A. 167:163, 1958. 3. Lewis, W. B.: California Med. 90:26, 1959. 4. O'Doherty, D. S., and Shields, C. D.: J.A.M.A. 167:160, 1958. 5. Park, H. W.: J.A.M.A. 167:168, 1958. 6. Plumb, C. S.: Journal-Lancet 78:531, 1958.

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Neurology Volume 9 • Number 10

Myasthenic syndrome in patients with amyotrophic lateral sclerosis

Donald W. Mulder, M.D., Edward H. Lambert, M.D., and Lee M. Eaton, M.D.*

DURING THE COURSE of their illness, patients with amyotrophic lateral sclerosis may have complaints of, and may demonstrate on clinical and laboratory examination, unusual muscle fatigability resembling that of myasthenia gravis. Other features of amyotrophic lateral sclerosis usually are sufficient to differentiate it from myasthenia gravis. However, it is important to recognize this occurrence of a myasthenic syndrome in amyotrophic lateral sclerosis to avoid confusion and uncertainty in diagnosis.

The presence of a significant defect of neuromuscular conduction in patients with diseases affecting the lower motor neurons has been suggested by others. Hamill and Walker[1] reported improvement of muscular strength after injection of neostigmine (Prostigmin) in patients with a variety of diseases of the motor system. In poliomyelitis, Buchthal and Höncke[2] observed unusual fatigability of motor units manifested in electromyographic studies by a gradual decrease in amplitude of their action potentials as seen during a sustained contraction. This was observed frequently in poliomyelitis by Pinelli and Buchthal,[3] but it was found only exceptionally in other diseases of the lower motor neurons. It was observed as early as the first ten days after onset of paresis in poliomyelitis. Hodes[4] concluded that this abnormality was explained best by the presence of a defect of neuromuscular conduction; this view was supported by the demonstration that use of neostigmine restored the amplitude of the action potential. A similar fatigue of motor units has been observed in syringomyelia,[5] amyotrophic lateral sclerosis[6] (Fig. 1), and other neurogenic atrophies. A myasthenic syndrome associated with neuromyopathy in carcinomatosis has been reported.[7]

It has become increasingly apparent that patients who have unusual sensitivity to curare or neostigmine and related drugs do not necessarily have myasthenia gravis. Rowland[8] concluded that it was not necessary to assume that all syndromes responsive to neostigmine have the same cause. Eaton and Lambert[7] stated that they no longer thought that positive results to tests for myasthenia gravis with neostigmine, edrophonium chloride, and curare are

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*Deceased.

in themselves pathognomonic of myasthenia gravis, although these drugs are useful in the diagnosis of myasthenia gravis.

We have observed occasional patients with amyotrophic lateral sclerosis in whom a definite myasthenic component to their illness was observed in their histories and physical examination and in the results of pharmacologic testing.[6] In some instances, these patients reported partial and transient relief of muscular weakness after oral use of neostigmine bromide.

We wish to report 4 cases of amyotrophic lateral sclerosis in which such a clinically demonstrable syndrome was present.

CASE REPORTS

Case 1. A 49-year-old farmer noted the onset of weakness in his right hand eighteen months prior to our examination. Shortly afterward, he experienced cramping pain in the small muscles of both hands following physical activity. The weakness gradually progressed, and he then noted difficulty in lifting objects with his right hand and some difficulty in climbing stairs. The weakness was made worse by activity and relieved by rest. Atrophy of the right arm and widespread fasciculation throughout his body musculature were noted.

Neurologic examination revealed hyperactive muscle stretch reflexes with no Babinski signs. Muscular atrophy, fasciculation, and weakness were observed in the right upper extremity, particularly in the right shoulder girdle. Atrophy and weakness also were observed in the lower extremities to a lesser extent. Sensory abnormalities were not present.

Examination of the cerebrospinal fluid revealed nothing abnormal. An electromyogram disclosed evidence of denervation and fasciculation in the muscles of all 4 extremities; the motor unit potentials were normal to large and were reduced in number. An increased proportion were polyphasic, and some varied in amplitude from moment to moment. The conduction velocity of nerves supplying the involved muscles was normal. A diagnosis of amyotrophic lateral sclerosis was established.

Testing of the involved musculature revealed unusual fatigability. An increased sensitivity to d-tubocurarine and edrophonium chloride was present. Following a test dose of one-fifth of a curarizing dose[9] of d-tubocurarine given intravenously over a period of five minutes, the strength of the right biceps decreased from 36 to 9 units, the strength of raising the straight left leg decreased from 30 to 12 units, and the grip of the right hand decreased in strength from 30 to 13 units. The left hand, which was not affected by the amyotrophic lateral sclerosis, showed no appreciable change. The maximal weakness in this patient occurred five to six minutes after the end of the injection of d-tubocurarine chloride, and recovery began twelve minutes later. The intravenous injection of 10 mg. of edrophonium chloride (Tensilon Chloride) restored the patient's strength to the previous level.

The patient was reexamined six months later, at which time progression of his illness, with dysarthria and difficulty in swallowing, was noted. A recent report from his family physician revealed further progression of his symptoms thirty months after the onset of the disease.

Case 2. A 36-year-old housewife noted the gradual onset of weakness in her lower extremities nine months prior to our initial examination. This weakness was associated with some muscular fasciculation. These symptoms had progressed.

We noted profound bilateral weakness of the lower extremities, particularly in the anterior tibial, the hamstring, and the iliopsoas muscles. There were no associated sensory findings or complaints. The muscle stretch reflexes were all hyperactive, except for the quadriceps reflexes, which were slightly diminished. An electromyogram revealed that the motor unit potentials in the weak muscles were slightly enlarged but were reduced in number and that they varied in amplitude from moment to moment. Evidence of denervation and fasciculation was observed in both the upper and lower extremities. The conduction velocity of nerves was normal. A diagnosis of amyotrophic lateral sclerosis was established.

The patient demonstrated unusual muscular fatigability, which was promptly reversed by rest. The intravenous injection of 5 mg. of Tensilon Chloride was followed by an increase in the strength of her hamstring and iliopsoas muscles beyond that seen at rest, although little if any change occurred in other muscles. The intravenous injection of one-tenth[9] of a curarizing dose of d-tubocurarine was followed by an increase in the weakness of raising the straight leg; at one-fifth of a curarizing dose, she had difficulty getting her heel off the bed, although she had experienced no difficulty in performing this test prior to the use of curare. In response to an intramuscular injection of 1.5 mg. of neostigmine methylsulfate, the patient had a definite increase in muscular strength.

It was reported ten months later that the patient was completely bedfast and had great difficulty in swallowing and talking.

Case 3. A 51-year-old farmer had noted the gradual onset of weakness in both arms eight months prior to our examination. Shortly thereafter, he also noted weakness in the muscles of the back.

We found muscular weakness and atrophy, with fasciculation apparent in both upper extremities and in the back. Fasciculation was present in the lower extremities, and the muscles of the anterior

compartment of the legs were weak. The muscle stretch reflexes of the upper extremities were hypoactive, but those in the lower extremities were normal. Abnormal reflexes were not observed, and there were no abnormal sensory findings or complaints. The electromyogram revealed evidence of denervation and fasciculation in the arms and legs. The action potentials of the motor units were large and reduced in number. An increased proportion were polyphasic. They declined in amplitude with continued contraction, particularly in the left biceps brachii. The conduction velocity of nerves was normal.

Exercise caused a rapid increase in his muscular weakness, which promptly improved with rest. The patient could flex his left arm against gravity and against slight resistance, but, after administration of one-tenth of a curarizing dose of d-tubocurarine, the patient no longer could flex the arm against gravity; this added weakness disappeared completely in thirty minutes. The subcutaneous injection of 1 mg. of neostigmine methylsulfate caused an appreciable bilateral increase in the strength of his arms but did not abolish the muscular weakness. The intravenous injection of 10 mg. of Tensilon Chloride caused prompt subjective and objective increase in the strength of the left biceps. The amplitude of the motor unit action potentials was better maintained during a sustained contraction.

The patient died sixteen months later from progression of muscular weakness with bulbar symptoms. Unfortunately, necropsy was not done.

Case 4. A 65-year-old aircraft inspector related that, eight months prior to our examination, he had noted the onset of atrophy, weakness, and fasciculation about the left shoulder that steadily progressed to involve the entire left arm. Four months later, he observed similar weakness and atrophy in the right arm. Two weeks prior to our examination, he first noted the onset of weakness in both lower extremities. Neurologic studies at 2 separate medical centers during the month prior to our examination had established a diagnosis of amyotrophic lateral sclerosis.

Our neurologic examination revealed weakness, atrophy, and fasciculation of all of the body musculature, more prominent in the upper than the lower extremities. Sensory abnormalities were not found. The muscle stretch reflexes were hyperactive in the lower extremities and diminished in the upper extremities. Abnormal reflexes were absent.

Electromyography disclosed evidence of diffuse denervation and fasciculation in the upper and lower extremities. The motor unit potentials were large and reduced in number, and many were polyphasic. Some of these potentials varied in size from moment to moment, suggesting a defect in neuromuscular conduction. The conduction velocities of the left ulnar and median nerves were normal. Repetitive stimulation of the musculocutaneous nerve revealed an abnormal decline in amplitude of response of the biceps brachii similar to that seen in myasthenia gravis. Biopsy of the left deltoid muscle, as reported by Dr. George Sayre, showed groups of atrophic muscle fibers, as well as scattered single atrophic fibers, and several muscle fibers that were undergoing floccular degeneration, some with phagocytosis.

Repetitive testing of muscles disclosed rapid weakening with exercise and prompt return to previous strength after a brief rest. The intravenous injection of one-tenth of a curarizing dose of d-tubocurarine revealed pronounced sensitivity of the muscles of the upper extremities to small doses of this drug. The strength of the biceps decreased from 7 units to 1 unit, and the strength of the grip decreased from 20 to 6 units. A dose of 10 mg. of Tensilon Chloride restored the patient's strength to its previous level.

A recent report from his family physician stated that, ten months after the onset of his illness, the patient died from respiratory failure secondary to inanition.

COMMENT

These 4 patients with classic amyotrophic lateral sclerosis presented some of the symptoms and findings of myasthenia gravis. In addition, electromyographic studies revealed

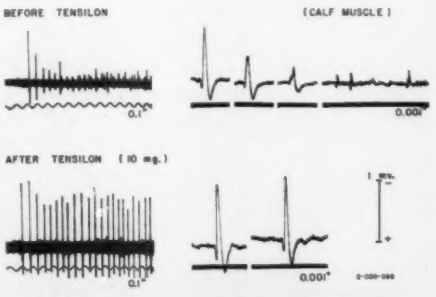

Fig. 1. Response to use of Tensilon Chloride in a patient with amyotrophic lateral sclerosis, showing the action potential of a motor unit during initiation of weak voluntary contraction of the gastrocnemius muscle. Before use of Tensilon Chloride, the amplitude of the action potential rapidly decreased (upper left). One minute after the intravenous injection of 10 mg. of Tensilon Chloride, the amplitude of the same motor unit action potential was better maintained (lower left). The sequence of events in a continuous record (time base, 10 cycles per second) is on the left. Detailed curves of the action potentials during the same contraction (time base, 1,000 cycles per second) are on the right.

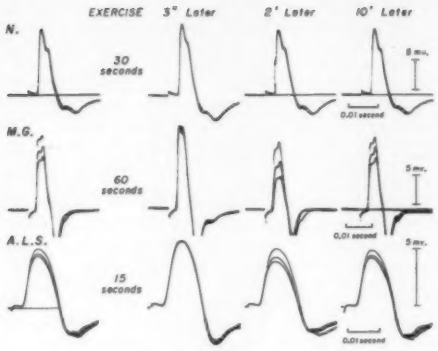

Fig. 2. Responses of muscle to maximal stimulation of motor nerve at a rate of 3 shocks per second before and after a brief period of voluntary contraction of the muscle. N. = normal person, showing the action potential of the hypothenar muscle in response to stimulation of the ulnar nerve. The responses were nearly exactly superimposed. M.G. = myasthenia gravis, showing the action potential of the hypothenar muscle in response to stimulation of the ulnar nerve. Before voluntary exercise of the muscle, the 3 responses declined progressively in amplitude. Three seconds after exercise, this defect was repaired and the initial amplitude was greater; two minutes later, the defect was more pronounced than it was prior to exercise; ten minutes later, the defect was nearly as it was prior to exercise. A.L.S. = amyotrophic lateral sclerosis, showing the action potential of the biceps brachii in response to stimulation of the musculocutaneous nerve. The sequence of events was like that seen in myasthenia gravis.

abnormalities suggesting the presence of a defect of neuromuscular conduction similar to that seen in myasthenia gravis (Figs. 1 and 2).

In our experience, this type of defect occurs frequently in patients who have amyotrophic lateral sclerosis. The myasthenic symptoms are most apparent in muscles seriously affected by this disease of the anterior horn cells, and perhaps for this reason the response to neostigmine and related drugs is not so dramatic as it is in myasthenia gravis. In the 4 cases reported here, the responses to administration of neostigmine methylsulfate, edrophonium chloride (Tensilon Chloride), and d-tubocurarine chloride were striking. The last patient experienced a threefold to sevenfold decrease in strength of the tested muscles after injection of one-tenth of a curarizing dose of d-tubocurarine. The latter effect was promptly counteracted by the use of edrophonium chloride. In all of the patients, injection of edrophonium chloride or neostigmine methylsulfate gave partial relief of the symptoms of weakness.

In selected patients with amyotrophic lateral sclerosis, the use of neostigmine is of distinct benefit. Our third patient was able to keep his head erect and was better able to use his upper extremities while taking neostigmine bromide orally. We have observed that other patients have had less difficulty in swallowing and talking while taking this drug. Unfortunately, use of neostigmine does not alter the course of the disease, and the patient frequently notes an alarming increase in fasciculation. It may be possible to accentuate the weakness of extremely weak muscles with an overdose of neostigmine; therefore, one must be cautious in its administration. The sensitivity to d-tubocurarine in certain patients who have amyotrophic lateral sclerosis suggests that this drug also should be used with caution.

The differentiation of myasthenia gravis from amyotrophic lateral sclerosis with a myasthenic response usually can be made without difficulty. In amyotrophic lateral sclerosis, the muscular atrophy, fasciculation, hyperreflexia, and relentless progress of the disease are usually more than sufficient to differentiate the 2 conditions. The pattern of electromyographic abnormalities, including evidence of denervation, fasciculation, and increased size but reduced number of motor units, is also an aid in diagnosis. Ptosis and diplopia, which are among the commonest symptoms of myasthenia gravis, are not features of the myasthenic syndrome associated with amyotrophic lateral sclerosis. However, difficulty in talking and swallowing is common in both diseases and may lead to confusion in diagnosis. In our experience, the myasthenic response, when present, is never so extensive or profound as is that found in some patients with myasthenia gravis. Usually, it is most apparent in weak and atrophied muscles.

The diagnosis of myasthenia gravis depends in part on pharmacologic tests.[10] Such methods for the diagnosis of myasthenia gravis have been used with increasing frequency since

1935, when the neostigmine (Prostigmin) test was introduced by Viets and Schwab.[11] In addition, the quinine test[12] and the Tensilon Chloride test[13] have become firmly established as valuable in the diagnosis of myasthenia gravis. In fact, it may be that some physicians depend too much on the outcome of pharmacologic testing, with the result that some nonmyasthenic patients are diagnosed erroneously as having myasthenia gravis. It is not our intention to discredit pharmacologic tests for myasthenia gravis; rather, we wish to emphasize that the myasthenic components in certain other conditions, such as amyotrophic lateral sclerosis, occasionally may be sufficiently prominent that the unwary person may be trapped into making an erroneous diagnosis of myasthenia gravis.

In certain patients with early amyotrophic lateral sclerosis, it is possible that the diagnosis could be confused with myasthenia gravis for a few months. The characteristic clinical findings of patients who have amyotrophic lateral sclerosis, with its relentless progression and incomplete response to neostigmine, and the results of electromyographic examination will allow one to make the proper diagnosis.

The occurrence of a myasthenic syndrome in amyotrophic lateral sclerosis and in other neuronal diseases suggests that abnormalities of the lower motor neuron itself result in a defect of neuromuscular conduction, which in many respects resembles that seen in myasthenia gravis. The mechanism of this syndrome in patients who have amyotrophic lateral sclerosis is still obscure. Studies on cats and rabbits in our laboratories[14] have demonstrated an increased sensitivity to curare in muscle that has been reinnervated after injury to nerves. It is possible that the recently described regenerating collateral fibers[15] and their motor end plates are unusually sensitive to curare and neostigmine and that this accounts for the myasthenic syndrome in amyotrophic lateral sclerosis. Alternative hypotheses include the possibility that disease of the motor cell body interferes with the synthesis or release of acetylcholine. It has been suggested[16,17] that the enzymes choline acetylase and acetylcholinesterase are synthesized in the nerve cell body and are carried to nerve endings via the axon.

SUMMARY

Because of the importance of the differential diagnosis, it must be recognized that symptoms in amyotrophic lateral sclerosis at times closely resemble those of myasthenia gravis.

The relentless progress of amyotrophic lateral sclerosis, with its muscular atrophy, fasciculation, and hyperreflexia, as well as electromyographic evidence of disease of the lower motor neurons, serves to distinguish it from myasthenia gravis. Ptosis and diplopia, which are common in myasthenia gravis, are not features of the myasthenic syndrome in amyotrophic lateral sclerosis.

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Experimental analysis of an attempt to improve speech in cases of expressive aphasia

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RECENTLY, REPORTS have appeared of what promised to be the greatest single advance in the treatment of aphasia since the disorder was first described. Briefly, the papers, by Birch and Lee[1] and by Birch,[2] described a dramatic improvement in the speech of 75% of expressive aphasics during and after binaural administration of a tone at 256 cycles per second at an intensity of 60 db. In the first paper,[1] 10 of 14 patients tested were reported to show performance that was "decisively improved" under auditory stimulation. Birch's results were apparently similar for an additional 21 patients tested in the subsequent study.[2]

The profound and dramatic improvement of speech resulting from so simple a procedure as auditory stimulation would have considerable theoretic and practical significance in the study of aphasia. Therefore, the following experiment was undertaken in an effort to replicate Birch's findings.

PROCEDURE

Patients. A total of 18 patients, 15 men and 3 women, ranging in age from 36 to 72, with an average age of 58, was studied. All were cases of expressive aphasia, with minimal or no receptive difficulties. The symptoms ranged in severity from mutism to moderate word-finding impairment. Some patients additionally demonstrated slight dysarthria. The diagnosis was cerebral vascular accident to the left hemisphere in 16 cases and neoplasm in 2. All patients were right-handed prior to onset of symptoms. They were tested from one to thirty-two months after onset of symptoms. Sources of patients were the Abraham Jacobi Hospital Rehabilitation Medicine wards, 13, and nursing homes, 2; the remaining 3 were out-patients. All patients were right hemiplegics or hemiparetics; some were additionally hemianoptic. The patients' speech rehabilitation experience ranged from a minimum of no formal speech training to a maximum of two years of speech therapy.

Method. All testing was done in a sound-reduced room. The patient was seated facing the examiner, who sat at the controls of an Allison audiometer, model 20-A. The patients were told that they would be asked to name objects or to read words or numbers. Earphones were placed on both ears, but the tone was not turned on. In each of 6 tests administered, the number of objects correctly identified or words or numbers correctly read was recorded, as well as the time required by the patients to respond correctly. The patient was allowed thirty seconds for each response. The first was an object-identification test. The following common objects were presented individually in order: fork, spoon, comb, key, knife, pipe, and padlock. The second was a picture-identification test of a knife, pen, comb, and fork. The third was a word-reading test, listing knife, automobile, picture, and cat. The fourth was a color-naming test. Rectangles approximately 1½ x ¾ in. were shown in red, green, black, yellow, and blue. The fifth was a number-reading test, containing 428, 73, 41, 1,569, 9, and 14. The final test required the patient to read the following sentence: All

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TABLE 1

MEAN CHANGES AND t TESTS BETWEEN CONDITIONS OF SILENCE AND AUDITORY STIMULATION FOR CORRECTNESS AND LATENCY OF RESPONSE

	Number correct Means				*Latency in seconds* Means			
Test	*Silent condition*	*Auditory stimulation*	*Difference*	t	*Silent condition*	*Auditory stimulation*	*Difference*	t
Object-naming	3.22	3.33	.11	.46	129.22	126.61	2.61	.41
Picture-naming	1.78	1.94	.17	1.88	73.49	70.10	3.39	.89
Word-reading	2.17	2.11	—.06	1.08	60.83	62.94	—2.11	.75
Color-naming	2.17	2.17	.00	.00	96.05	94.87	1.17	.18
Number-reading	3.11	2.67	—.44	1.50	104.88	114.54	—9.89	1.24
Sentence-reading	4.06	2.94	—1.11	2.07	69.50	73.61	—4.11	.81

NOTE. Negative mean differences for Number Correct indicate that performance was poorer under conditions of auditory stimulation; analogous negative values for latency indicate that time before responses increased under auditory stimulation. None of the t values reach the .05 level of significance (2.11).

through the night the car sped swiftly down the road. On the final test, the number of words correctly read in sequence was noted. The patient was given one hundred seconds in which to respond, and the time he required was recorded.

After completion of the test under the silent condition, a tone of 250 cycles per second at 60 db was turned on for thirty seconds. At the end of this time, the test was repeated as before, with the binaural stimulation continuing throughout. If there was a question of hearing loss, audiometry was first conducted. In all cases in which hearing loss was demonstrated, the intensity of the tone was appropriately increased for each ear individually to insure that the patient was binaurally stimulated at 60 db above threshold.

The data were analyzed with a series of t tests for correlated means between silent and auditory stimulation conditions. That is, the averages of the group were compared for correctness of response and for latency of correct response under the silent condition and under auditory stimulation.

RESULTS

Table 1 summarizes the data of the experiment. In the column headed "Silent Condition" under "Number Correct" are given the average number of correct responses of the group of patients for each of the 6 tests. The patients were, on the average, correct on approximately half of the identifications and word or number readings. They could read about 4 words in the sentence correctly in sequence. Under the condition of auditory stimulation, very little difference was noted. Thus, of the 6 tests, the group improved very slightly on 2, remained the same on 1, and became slightly worse on the remaining 3. However, none of the differences between the silent and the auditory stimulation conditions was statistically significant at the 5% level of confidence. The only difference which approached significance was that for the sentence-reading test. Here the group was able to read about 1 word less on the average under auditory stimulation than they could before the sound was administered. Essentially the same results can be seen if one compares

TABLE 2

FREQUENCY OF PATIENTS SHOWING ANY "IMPROVEMENT" FOR ACCURACY AND LATENCY OF RESPONSE

Total number of tests	*Number of patients showing "improvement"*	
	Accuracy	*Latency*
None	10	7
1	5	3
2	2	3
3	0	2
4	1	1
5	0	1
6	0	1
Total	18	18

NOTE. The figures in the 2 right columns refer to numbers of patients who showed any "improvement" with regard to either correct identification or decreased time of response. The left column indicates the number of tests on which this "improvement" was shown.

the group for latency of correct response on each of the tests. That is, the group responded, on the average, from one to three seconds more quickly on 3 of the tests and from two to ten seconds more slowly on the remaining 3 tests under the auditory stimulation condition. However, none of these changes in latency of response was statistically significant.

The possibility remained that these negative results could be attributed to a small proportion of the group who did not improve and that their poor score masked improvement of other members of the group. To test this possibility, a tally was made of the subjects who "improved"* on all 6 of the tests, 5, 4, and so on down to none of the tests. This was done for both accuracy of response and latency of response. Table 2 gives these data. It can be seen that 10 of the 18 patients "improved" on no tests, that is, they remained the same or became worse on all tests; 5 "improved" on only 1 test; 2 "improved" on 2 tests; and only 1 "improved" on as many as 4 tests. A slightly greater number of patients "improved" with regard to latency. However, the hypothesis that at least some patients showed a marked improvement was not verified. Only a small proportion showed any "improvement" and these patients showed it slightly, on only 1 item in all but 2 cases.

*"Improvement" as used here merely means any increase in score from the silent to the stimulation condition, regardless of how slight. Thus, the greatest "improvements" which occurred were 3 additionally correct object identifications for 1 patient and 2 additionally correct picture identifications for another. No other "improvement" was greater than 1 for any patient on any test. However, the auditory stimulation condition resulted in a lessening of scores in 10 patients, ranging from 1 to 7, on all tests; 6 of these patients showed poorer scores by at least 2 points on one or more tests.

To check this possibility more directly, the patient who showed slight improvement on 4 of the tests for accuracy of response and on five for latency of response was retested a week later. The retesting was done in the same fashion as the initial testing; the objects were identified under the silent condition and then under auditory stimulation. This time, the patient's performance remained at the same level on 2 tests, became poorer on the remainder for correctness of response, and became worse for latency of correct response on all tests.

Table 3 gives the frequency of patients showing any "improvement," becoming worse, or remaining the same on each test during auditory stimulation for correct response and for latency of correct response. It can be seen that on each test during auditory stimulation, the greatest number of patients showed the same performance that they did during the silent condition. This number ranged from 9 patients on the test of object recognition to 17 patients on the word-reading test. On 3 of the 6 tests, more patients became worse during auditory stimulation than "improved."

A difference between the studies of Birch and the present investigation is that the duration of illness was a minimum of two years in Birch's patients and that, for 13 of the 18 patients in the present study, the onset of symptoms occurred less than two years before testing. In order to determine whether the duration of the illness was related to the magnitude of "improvement," patients with varying durations of illness were compared according to the number of tests on which they showed any degree of "improvement."

TABLE 3

FREQUENCY OF PATIENTS BECOMING WORSE, REMAINING THE SAME, AND IMPROVING ON EACH TEST UNDER AUDITORY STIMULATION

Test	*Became worse*		*Stayed same*		*"Improved"*	
	Correct	*Latency*	*Correct*	*Latency*	*Correct*	*Latency*
Object-naming	4	5	9	5	5	8
Picture-naming	1	6	14	7	3	5
Word-reading	1	4	17	9	0	5
Color-naming	3	7	11	7	4	4
Number-reading	3	5	14	8	1	5
Sentence-reading	4	4	14	11	0	3

NOTE. The total number of patients is 18 for each test, summed separately for "Correct" and for "Latency."

In the patient showing "improvement" on the greatest number of tests, 4, the onset of symptoms occurred only three months prior to testing. In the 2 patients showing the next greatest "improvement," on 2 tests, the onset of symptoms preceded testing by one month and twenty-four months, respectively. The group was then divided into 2 subgroups: those in whom the duration of symptoms was less than one year and those in whom it was more than one year. It was found that 6 of the 11 patients with less than one year's duration of illness showed any "improvement," whereas only 2 of the 7 patients with duration of illness greater than a year showed any "improvement."

COMMENT AND CONCLUSIONS

It is difficult to account for the failure of this study to confirm the results of Birch.† In contrast to his findings of improvement in 75% of aphasic patients under auditory stimulation, none of the patients in the present study was found, under the same conditions, to exhibit more than what appear to be chance fluctuations. The patients appear to be similar in the 2 investigations, since all but 2 of the patients in the current series suffered from cerebral vascular accidents, as did those in Birch's series. Although the duration of illness was greater in Birch's series, the differences in the results cannot readily be attributed to this factor; it was found in the present experiment that the patients showing the greatest "improvement," however slight, were those with *lesser* duration of symptoms. A minor variant in the procedure was that 256 cycles per second was used as the stimulating tone in Birch's experiment, whereas 250 cycles per second was used in the present experiment.

In conclusion, the author has failed to confirm any improvement in the ability of expressive aphasics to speak during binaural stimulation. The author has no explanation to offer for this lack of confirmation.

SUMMARY

This study was an attempt to confirm Birch's finding that intensive binaural stimulation of expressive aphasics causes dramatic and immediate improvement of their speech. A group of 18 expressive aphasics was tested for accuracy and latency of correct response on object-naming, picture-naming, word-reading, color-naming, number-reading, and sentence-reading tests. Immediately thereafter, they were stimulated binaurally with a tone of 250 cycles per second at 60 db for thirty seconds and then retested with stimulation continuing. Neither the group *nor any individual patient* demonstrated improvement on any test. Chance fluctuations in performance adequately describe the results of the stimulation. The author has no explanation to account for the failure of this study to confirm Birch's results.

The author is deeply indebted to Miss Marilyn Silver, speech and hearing therapist of Jacobi Hospital, for her painstaking evaluation of the speech and auditory status of all patients studied in the present experiment.

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†It must be noted at this point that the "independent confirmation" of Birch's findings attributed to Cherry[2] could be verified neither by referral to the article quoted by Birch[1] (p. 3851) nor by personal communication from Cherry.

Experimental mutism resulting from periaqueductal lesions in cats

John Adametz, M.D., and James L. O'Leary, M.D.

AKINETIC MUTISM was described and named by Cairns and associates,[1] who presented a case. The syndrome can be reduced principally to mutism, loss of voluntary and emotional movement excepting that of the eyeballs, and apparent loss of emotional feeling. In their case, the condition had resulted from an epidermoid cyst of the third ventricle; they noted the similarity to case reseulting from chronic encephalitis of the von Economo type reported by Richter and Traut.[2] Bailey and Davis[3] cited the similarity to still other cases described at about the same time by Bailey, Buchanan, and Bucy.[4]

Bailey and Davis[3,5] and Bailey[6] reported that the essentials of akinetic mutism could be reproduced experimentally by a lesion in the periaqueductal (central) gray. These lesions were made by passing a flexible electrode forward through the fourth ventricle. Corresponding results were obtained in cat and monkey. Cats with lesions of lesser size appeared wild, showed dilated pupils, stared vacantly into space, and struck out as though at imaginary menacers. More extensive lesions caused them to lie "silent and flaccid as a wet rag."

Skultety, Meyers, and Brown[7] studied cats with central lesions, some produced by the flexible electrode technic of Bailey and Davis[3,5] and others by the Horsley-Clarke routine; the animals gradually reacquired the general behavioral characteristics of their preoperative status, the only persistent alteration being a slight postural and coordinative deficit of the limbs, more apparent in the posterior pair. Later, Ross-Duggan and Richland[8] reported the production of akinetic mutism in cats by electrocoagulation of the periaqueductal gray. In their animals, there was electroencephalographic evidence of wakefulness and only minimal rigidity. At the same meeting, Skultety[9] reported investigations of the effect of periaqueductal lesions upon vegetative functions of the cat. His results were negative for the functions tested. Recently, Melzack, Stotler, and Livingston[10] have reported upon lesions of the central gray in 5 cats prepared for conditioning. Loud vocalization occurred upon placement of lesions, and mutism was evident subsequently.

Another relevant experimental study was that of Magoun and associates.[11] By electrical stimulation of localized areas in the midbrain and pons of the lightly anesthetized monkey and cat, they obtained coordinated facial and vocal activity on the whole closely resembling that seen and heard during the expression of unpleasant emotion by a normal animal. In both cat and monkey, the reactive area of the midbrain included the central gray and a bridge of tissue extending through the dorsal and into the lateral and ventral parts of the tegmentum. In cats, Kelly, Beaton, and Magoun[12] also examined the effects of midbrain lesions which destroyed the central gray and the adjoining tegmentum, abolishing or reducing faciovocal behavior. Their evidence pointed to a central midbrain integrating mechanism for faciovocal behavior in emotional expression and recalled an earlier clinical study by Wilson.[13] This differentiated between an emotional and a volitional component of faciovocal functioning in man and hypothesized for the emotional component a path skirting the thalamus mesially and ventrally. Another relevant past study is that of Gibbs and Gibbs,[14] who described a purring

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Fig. 1. Photographs of the 6 cats described, each taken shortly before death. All except No. 17 were mute and failed to purr postoperatively. That cat showed only minor encroachment upon the periaqueductal gray.

center in the infundibulum of the cat's hypothalamus isolated by stimulation with a Harvard inductorium.

The present study supports the most recent findings of Skultety and Meyers[15] indicating that mutism, but not akinesia, is a feature of lesions placed in the central gray. In addition, we have uniformly observed a significant increase in appetite postoperatively.

OBSERVATIONS

A series of case reports and 3 figures are presented. Figure 1 shows the alert postoperative appearance of 5 mute animals and of

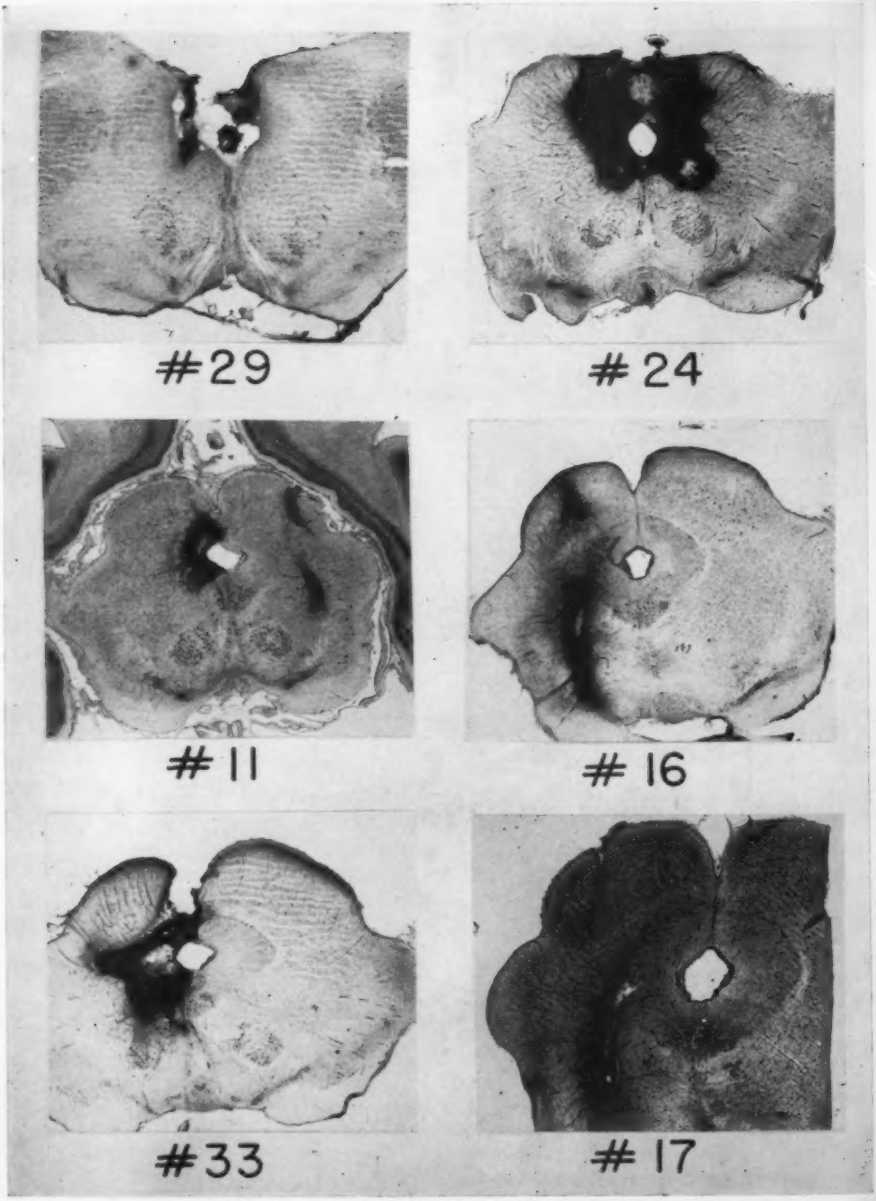

Fig. 2. Photographs of frozen, thionine-stained transverse sections from the brain stems of the 6 cats illustrated in Figure 1. The section selected indicates the maximum size of the lesion in each.

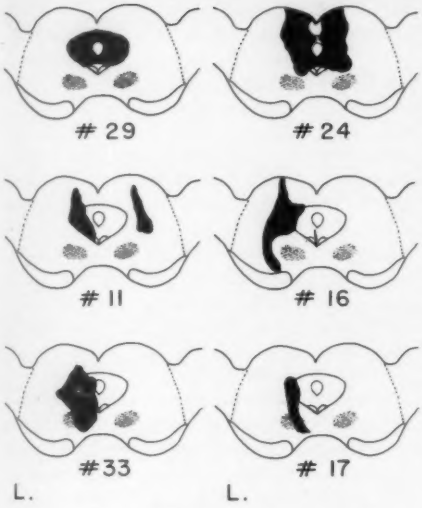

Fig. 3. Plots indicative of the size of the lesions to compare with the photographs of Figure 2

1 other with a lesion which encroached upon the central gray without producing mutism. Figure 2 shows the histologic appearance of each lesion at the level of most extensive damage. Corresponding sketches of the configurations of the lesions are shown in Figure 3.

All animals were kept under close observation for a ten-day period preceding the placing of the lesions. This included (1) the daily feeding, (2) inspection of unrestrained activity including traverse of 1 and 3 in. horizontal ladders, (3) handling, and (4) still and motion picture photography. Regular observation was continued postoperatively, and, in addition, each animal's reaction to birds and mice was tested at intervals.

CASE REPORTS

Cat 29. Preoperatively, she was very friendly and coordinated and kept herself well groomed. She ate well but not excessively, was attentive to birds and mice, and mewed and purred upon petting or being let loose in the room. On November 9, 1957, a bilateral longitudinal coagulation was placed in the central gray. The animal recovered rapidly, and, as early as the first postoperative day, she paced the room and ate without prompting. She remained playful but became permanently mute and did not purr during her one hundred twenty-two day survival period. Even a painful stimulus did not evoke a cry. She developed an excessive appetite within seven days after the placing of the lesion, and this persisted. She was normal neurologically and exhibited excellent coordination in walking the horizontal ladders and in catching mice. She was killed to obtain histologic confirmation of the site of the lesion.

The lesion, which proved to be 1.5 mm. in diameter and 2 mm. long, extended caudally from the opening of the aqueduct into the third ventricle. It was almost confined to the central gray, and only ventrally did it encroach upon the reticular substance.

Cat 24. She was a friendly, playful cat and was excited easily by mice placed in her cage. She mewed and purred regularly during the observation period, was clean in her eating habits, and groomed herself well. A 1-stage, bilateral longitudinal coagulation of the central gray was made, the animal recovering rapidly and uneventfully. Except for equally dilated pupils, there were no postoperative neurologic signs. On the first day after the operation, she walked about the room, approached her food, and ate it. She was never observed to mew or purr again, nor did she make an outcry when given a painful stimulus. Her appetite became excessive within nine days postoperatively, and this persisted. She was killed one hundred eighty-three days after the coagulation.

The lesion had involved the entire cross section of the central gray at the level of the middle of the superior colliculus. At its periphery, it extended somewhat into the outlying reticular substance laterally and ventrally and into the medial quadrigeminal plate dorsally. Its total dimensions were 4 x 3 x 3 mm.

Cat 11. This cat was reasonably clean preoperatively and performed well upon the horizontal ladders. His appetite was good. When anyone entered the room, he moved to the front of his cage and began to mew. Unrestrained, he was regularly attracted by a bird in a cage.

On September 7, 1957, the first stage of a bilateral 2-stage operation was done, placing a lesion which later was shown to involve the left wall of the cerebral aqueduct and to extend ventrally into the reticular substance. Thereafter, the cat was quite lethargic for several days and the left pupil was dilated. His foreleg gait was broad-based, and the occiput was cocked to the side of the lesion; he circled to the left in walking. His ataxia cleared rapidly, and, by the fifth postoperative day, he was alert and responsive. He ate and drank without aid and watched a bird attentively. However, he was mute and no longer purred, this continuing until his death on the eighty-second day following the second operation. It is important that the mutism followed the first stage operation, since it was shown histologically that the second stage coagulation did not enter the central gray. After the second stage procedure, the animal improved more rapidly than following the first stage. Following the second stage on September 20, 1957, the circling and cocking of the head which developed after the first operation disappeared and his pupils became equally dilated. He continued to be neat in appearance, but his behavior became hyperkinetic, so that, when unrestrained, he either paced back and forth, pranced about continually, or followed the observer from room to room. His appetite became excessive within six days following the first operation.

On December 11, 1957, this animal, then in the best of health, had his first generalized seizure, which was strongly opisthotonic in character and lasted for fifteen minutes. The animal did not recover and died within four hours.

The lesions were found to be well healed, and there was no evidence of recent hemorrhage, which was found in some other cats that died of a midbrain lesion, to account for the seizure or the death. Both left and right lesions extended somewhat more rostrally than expected, reaching the rostral border of the habenulopenducular tract and entering the caudal margin of the thalamus. The left sided lesion extended caudally along the lateral border of the central gray, destroying it but leaving its dorsal bridge intact. It was 1.2 x 2 mm. in diameter and 6 mm. long. From the central gray, the lesion passed ventrally through the intermediate reticular substance reaching to the dorsal surface of the cerebral peduncle. The aqueduct showed a grade 1 dilation. The size of the right sided lesion was comparable, but it did not involve the wall of the aqueduct; it is not described in detail because the mutism developed following the placing of the first stage, left sided lesion.

Cat 16. This clean male cat of medium size was playful and mewed and purred when stroked. He performed complicated maneuvers in a skilled fashion and was attracted by mice placed in his cage.

A 1-stage, bilateral coagulation was so placed as to destroy the central gray, but it was misdirected. Postoperatively, the pupils remained equal in size and the stance was entirely symmetric. In a few days, the animal appeared to have entirely regained the preoperative status of his neuromuscular control. However, his appetite became excessive within seven days postoperatively, and he neither purred, mewed, nor cried in response to a painful stimulus. He was killed on the two hundred fifty-eighth postoperative day to obtain histologic verification of the site of the coagulation.

A unilateral lesion was evident at the midcollicular level extending 0.5 mm. into the lateral expansion of the central gray and passing 4 mm. downward through the reticular substance to the subthalamic region. At its greatest width, this extension of the lesion was 1 mm. across.

Cat 33. The animal was clean, mewed frequently, and purred when petted. He was alert, ate well but not excessively, and was attracted by mice placed in his cage. On November 27, 1957, an extensive 1-stage lesion was placed unilaterally at the midlevel of the superior colliculus. He recovered slowly; by the second postoperative day, he was able to stand but circled to the left. The circling subsided, and he began to eat solid food unaided. He developed an excessive appetite within ten days postoperatively. He neither purred nor mewed during his postoperative period. He could catch mice with alacrity, although, when not stimulated, his behavior was somewhat listless. He died March 13, 1958, within a few hours after a generalized seizure and one

hundred and four days after the lesion had been placed.

There was a chiefly unilateral lesion at the superior collicular level situated in the rostral third of the central gray. Its size was 3 x 2.5 mm., and it involved only 1 side. A ventral outpouching extended through the neighboring third nerve nucleus to the dorsal edge of the rostral end of the red nucleus. Another outpouching entered the lateral reticular substance. The lesion extended forward to the caudal margin of the thalamus.

Cat 17. For completeness, this brief summary is included about a cat in which a 1-stage coagulation had been made in the intermediate reticular substance of the rostral midbrain. This encroached upon the lateral expansion of the central gray at the midlevel of the superior colliculus but was otherwise confined to the reticular substance. The recovery of this animal was similar to that of the cats described previously, but it did not become mute and its appetite was unaffected. It lived twenty-five days. This result should be compared with those in cats No. 16 and 33, which also had incomplete central gray lesions and yet became mute.

In 43 cats in which extensive bilateral reticular lesions were placed for other purposes, the lesions did not encroach upon the central gray. These cats did not become mute and continued to purr postoperatively. Their appetites were unchanged.

DISCUSSION

Besides supporting Skultety and associates [7,9,15] on the occurrence of mutism with central gray lesions of the cat, we agree that, for mutism to develop, it is not necessary that the entire central formation be destroyed. None of our lesions involved the length of the aqueductal wall and only 2 its entire cross section. Besides their corroborative value, our findings show that even unilateral or otherwise incomplete lesions may produce mutism. It was more difficult to prove that a lesion large enough to occasion mutism did not encroach significantly upon the tegmentum. We had complete confidence in that in only one of our animals, No. 29. In another, No. 24, the lesions extended dorsally into the quadrigeminal plate and ventrally minimally involved the tegmentum bilaterally. With respect to the minimum size a central lesion need be to result in mutism, the smallest we had was the unilateral lesion of cat No. 16, which, however, also involved the tegmentum extensively, although in cats No. 11 and 33 only 1 side of the aqueductal wall was affected. A tegmental lesion may encroach upon the central gray without causing mutism, but, as in our cat No. 17, such encroachments have been small. In another large series of cats, in which the tegmental lesions did not encroach upon the central gray, mutism did not occur.

Purring is separated from other evidence of vocalization because it suggests a pleasant state of feeling. Since our cats that lost their ability to purr postoperatively gave other signs of satisfaction, the motor integration of purring rather than ability to express satisfaction appeared to be interfered with. By electrical stimulation, Gibbs and Gibbs[14] found a purring center in the cat hypothalamus and Graham Brown[16] produced a modification in respiration akin to laughing in a chimpanzee with a sectioned brain stem; these results seem to support the preceding interpretation. Expressions suggestive of pleasant feeling are not the ordinary result of stimulation of the central gray, however. More usually, accompaniments linked with unpleasant affect, as yowling and spitting, have been reported.[11] MacLean[17] also observed yowling and spitting upon chemical stimulation of the central gray, and Bailey and Davis[3,5] reported it as a result of their less extensive lesions. If a purring center is situated in the infundibulum, a descending fiber system might conceivably pass downward near the central gray, although the shivering path of Birzis and Hemingway,[18] also of hypothalamic origin, is significantly removed from it.

We have found no evidence in the literature of mutism associated with lesions placed more rostrally than ours. Schreiner and coworkers[19] report that cats with lesions of the anterior thalamic nuclei appear oversolicitous to pleasurable stimuli, responding with loud purring, whereas those with lesions of the mediodorsal nuclei display episodic spitting and yowling when handled. However, several of the latter cats did develop voracious appetites. Nor did Bond and associates[20] pro-

duce results similar to those reported here with posterior septal, fornical, or anterior thalamic lesions in cats.

SUMMARY

A series of 5 cats was made mute by electrolytic lesions which destroyed a part or the whole of the cross section of the cerebral aqueduct. The animals also lost their ability to purr, and their appetites increased markedly. In a large series of cats with neighboring tegmental lesions which did not encroach upon the central gray, these signs of deficit did not obtain.

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Vascular insufficiency of brain stem and spinal cord in spinal trauma

Richard C. Schneider, M.D., and Elizabeth C. Crosby, Ph.D., Sc.D.

IN THE STUDY of the relationship of spinal trauma to the resultant acute and chronic damage to the brain stem and spinal cord, some clinical and pathologic features cannot be explained readily on the basis of the initial traumatic lesion. A remote or secondary clinical or pathologic effect often is present which requires further explanation. Evidence accumulating in the literature suggests that these facts may be related to the peculiarities of the vascular supply to the brain stem and spinal cord.

The task of describing briefly the normal circulation of these areas is almost impossible when one reviews the immense volume of literature on the subject. A group of references will be cited without too great amplification of the subject matter, so that the reader does not become so lost in anatomic details that correlation with the clinical aspects of the problem is forgotten. Adamkiewicz,[1] Kadyi,[20] and Ross[31] contributed the outstanding fundamental work on the vascular supply of the spinal cord during the last twenty years of the nineteenth century. With the exception of the paper written by Stopford[42] and a few other scattered articles, more than thirty-five years elapsed before interest in the subject was rekindled by Alexander and Suh,[2] Bolton,[7] Herren and Alexander,[16] Klaue,[22] Sahs,[33] Suh and Alexander,[43] Tureen,[46] Yoss,[48] and Zülch.[49] The culmination and condensation of much of their extensive investigations are ably presented in two texts, Mettler[27] and Bing.[6]

NORMAL CIRCULATION

The vertebral arteries climb upward in the neck behind the common carotids entering the sixth intervertebral foramen (Fig. 1). They wind about the massa lateralis atlantis, perforating the dura and entering the skull at the lateral margins of the foramen magnum. The posterior inferior cerebellar arteries branch off bilaterally a short distance from the point where the vertebral arteries enter the cranium. The vertebral arteries fuse to form the basilar artery which proceeds upward and forward in the basilar sulcus of the pons, giving off its paired branches: the lateral arteries of the medulla, the anterior inferior cerebellars, the in-

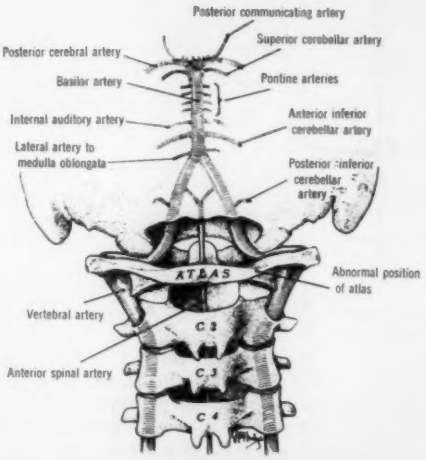

Fig. 1. The diagram shows the vertebral and basilar circulation with [1] the vertebral arteries proceeding through the intervertebral foramina; [2] the point of compression at C1 intervertebral foramina and at the occipital condyle when dislocation of the atlas occurs; [3] the origin of the anterior spinal artery; and [4] the main branches of the basilar artery.

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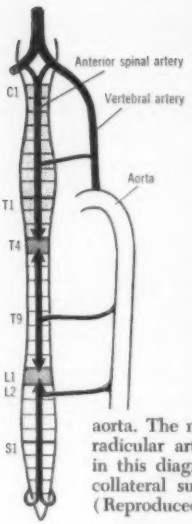

Fig. 2. The diagram shows origins of anterior spinal artery from vertebral artery bilaterally. Anterior spinal artery supplies anterior two-thirds of cervical spinal cord and uppermost thoracic segments to T4 level. Blood flow is caudal. Collateral supply is poor in region of T4 neural segment, so that hypoxia may cause infarction here in the distribution of the anterior sulcal arteries with central cord destruction. Remainder of arterial supply for thoracic cord from T4 to L1 is by intercostal branches from aorta. The major one, the great ventral radicular artery, enters at T9 segment in this diagram. Another zone of poor collateral supply is at L1 dermatome. (Reproduced from Bing.[6])

ternal auditory arteries, the perforating pontine branches, and the superior cerebellar arteries. At the upper margin of the sella turcica, the basilar artery splits into its terminal branches, the posterior cerebral arteries.

In the cervical or distal portion of this cervicomedullary circulation are paired branches of the vertebral arteries, arising prebasilarly, which unite in the midline to form the anterior spinal artery (Fig. 1). This vessel extends caudally along the anterior surface of the spinal cord, narrowing somewhat near the upper thoracic segments (T4).

The lateral spinal arteries are a single set of branches of the vertebral artery[27] which are extremely variable (Fig. 2). They pass through the intervertebral foramina of the lower cervical and upper thoracic vertebrae, supplying the C7 through T2 spinal cord segments. On the basis of anatomic studies, Bolton[7] has indicated that the poorest collateral circulation of the cord is at a zone between the T1 and T3 segments. Zülch,[49] on the other hand, said that the T4 segment is the critical area of poor blood supply (Fig. 2). Both authors noted that the flow in the anterior spinal artery is in a cephalocaudad direction on both the anterior and posterior surfaces of the spinal cord.

The prolongation of the anterior spinal artery in the thoracic area below the T4 neural segment has been designated as the anterior medial spinal artery by Yoss.[48] The segmental arteries from the aorta which supply the thoracic segments of the spinal cord to the level of the L1 segment are the intercostal arteries. Adamkiewicz[1] designated one of the latter, which is routinely the largest, as the arteria radicularis anterior magna, and Mettler[27] described it as the great ventral radicular artery; it presumably enters at a point between the T8 to L4 segments. Bolton[7] and Zülch[49] think that this vessel enters at the T9 segment. The direction of blood flow is upward to the T4 segment and caudally to the L1 segment where, according to Zülch, there is another level of poor collateral circulation (Fig. 2). Bolton, however, believes that the blood flow is only in a caudal direction.

In the lumbosacral area, the radicular arteries are derived from the lumbar, iliolumbar, and lateral sacral arteries. The major vessel, in most opinions, appears to enter the intervertebral foramina at L2 to form the lowermost portion of the anterior spinal artery, called the terminal artery, which runs along the filum terminale.[27] The blood flows cephalad for 1 segment and then caudally to the conus medullaris. According to Tureen,[46] the arteries of the 2 lumbar nerve roots and the 5 sacral nerves fail to reach the spinal cord and are concerned primarily with supplying the anterior and posterior nerve roots of the cauda equina.

The posterior spinal arteries, which are sometimes called the posterolateral spinal arteries, receive branches from the posterolateral arterial plexus[27] at various levels. These vessels are paired and are considerably smaller than the single large anterior spinal artery. In the posterior spinal arteries, the blood flow is toward the thoracic area in the cervical segments, with a zone of poor vascular supply at T1-T3 segments. However, in the lower thoracic, lumbar, and sacral areas, Bolton[7] has indicated that the blood flows cephalad toward the upper thoracic segments. In the region of the conus, Kadyi[20] describes an artery, the ramus anastomoticus arcuatus, which is a communicating vessel between the posterior and anterior spinal arteries.

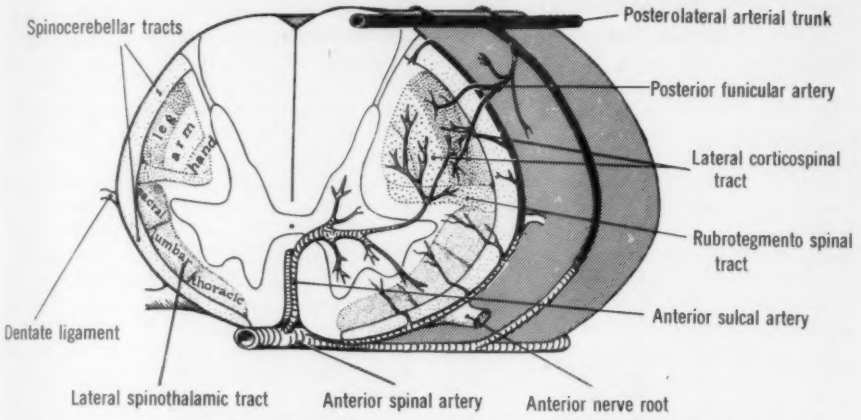

Fig. 3. A cross section of the cervical spinal cord shows the anterior spinal artery with its anterior sulcal branch, which supplies the anteromedial two-thirds of one-half of the cervical spinal cord at any given segment. The peripheral branches from the arteriae coronae supply the region of the lateral spinothalamic tract of the anterolateral portion of the spinal cord. The leg area in the lateral corticospinal tract is supplied by the posterior funicular artery. The arm and hand portion of this tract and the rubrotegmentospinal tract are supplied by the anterior sulcal vessel. The lateral spinothalamic tract receives much of its blood supply by the arteriae coronae. There are numerous variations in this vascular supply.

Thus far, discussion has involved the vessels of the spinal cord which course more or less in a longitudinal plane. There are, however, many smaller branches which supply the cord in a sagittal plane (Fig. 3). Arising from the anterior spinal artery at various levels along the cervical and thoracic cord are vessels lying within the anterior sulcus which extend upward and laterally to supply the anteromedian portion of the spinal cord. Herren and Alexander[16] have designated these as anterior sulcal arteries which supply the anterior and lateral columns on either side of the cord. At any given segment, only 1 side of the cord is supplied by this vessel. Bolton[7] has indicated that the posterior spinal arteries supply the posterior white columns and the more posterior part of the posterior grey columns.[40]

Segmentally, arteries are given off from the intercostal vessels or lateral spinal arteries which enter the intervertebral foramina and dorsal and ventral radicular arteries which accompany the posterior and anterior nerve roots, respectively. These unite with the posterior and anterior spinal arteries directly and then are joined together segmentally along the periphery of the spinal cord as the arteriae coronae (Fig. 3). Tureen[46] has stated that the collateral of these vessels is poorest in the vicinity of the lateral columns. From these arteriae coronae, branches extend inward along the periphery of the cord supplying the posterolateral and anterolateral portions of the cord. Suh and Alexander[43] reported that the only completely efficient radicular arteries are present at the C6, T10, and L1 neural segments.

Upon this sagittal section of the spinal cord, the authors would like to superimpose the various fiber tracts which are so important neuroanatomically and clinically (Fig. 3). The anterior sulcal or anterior commissural artery supplies the anteromedial gray, the rubrotegmentospinal tract, and the more medial portion of the lateral corticospinal tract including the hand and arm areas. The leg area of the lateral corticospinal tract receives its blood flow through the posterior funicular branch from the posterior spinal artery or the arteriae coronae. The region of the lateral spinothalamic tract on the periphery of the spinal cord is supplied by the small branches of the arteriae coronae from the periphery of the spinal

cord. It is these relationships which are so important in the anatomic, pathologic, and clinical correlations.

Either acute or chronic trauma to the spinal cord with associated impairment to the blood supply of the brain stem or spinal cord was present in 5 cases reported here. Vascular insufficiency in the region of the cervicomedullary junction apparently occurred in 3 patients. A fourth case had decreased blood supply to the cervical and upper thoracic spinal cord, while the fifth patient demonstrated the problems associated with middle and lower thoracic spinal cord vascular insufficiency.

The cervicomedullary junction is a no man's land which has been inadequately examined in life by clinicians and is shunned in death by pathologists. It is the authors' firm conviction that a transient or permanent impairment of the vertebral blood supply to the brain stem or cervical spinal cord may be responsible for those fatal cases of acute craniocerebral trauma which, at postmortem examination, show no apparent pathologic cause of death.

The various neurologic symptoms referable to spasm or occlusion of the vertebral or basilar arteries have been described by numerous authors.[9,11,17,18,24,25,29,39,41,44,47]

The variation in the neurologic pattern may be explained by the extent and duration of the occlusion and the distribution of the vessels. Tureen[46] has shown experimentally in occlusion of blood supply to the cord that "ischemia of 15 minutes is accompanied by functional and histological changes which are reversible. Periods of ischemia longer than 20 minutes result in irreversible anatomical and physiological changes."

The literature contains many references to atlantoaxial dislocations with or without myelopathy.[3,12,21,40,45] It is interesting that only a relatively few articles suggest that the neurologic symptoms or myelopathy were due to impairment of the vascular supply of the brain stem and spinal cord. Bachs and associates[3] presented a case of delayed myelopathy following atlantoaxial dislocation and cited 8 other such cases in the literature. They mentioned the "importance of the vascular factor in the pathogenesis of the myelopathy" but made no indictment of any specific vessel, such as the vertebral artery and its branches. Ford[13] reported on a patient with syncope, vertigo, and visual disturbances following intermittent obstruction of the vertebral arteries due to a defective odontoid process with excessive mobility of the second cervical vertebra. Four years later, Ford and Clark[14] presented 2 other cases in which there was manipulation of the neck with thrombosis of the basilar artery and softening in the cerebellum and brain stem. They believed that an intermittent or partial obstruction of the blood flow in the vertebral artery led to a secondary thrombosis of the basilar artery higher up in the circulation. Their impression was that the vascular insufficiency and symptoms were not necessarily due to manipulation but might have been produced simply by the patient's turning his head in certain positions. Pratt-Thomas and Buerger[29] have called attention to the fact that, in their 3 reported cases, there was probably vertebral and basilar artery occlusion with vascular insufficiency on cervical manipulation without fracture-dislocation of the cervical spine. Hutchinson and Yates[17,18] indicated that, even though the carotid or vertebral artery was not occluded completely, vascular insufficiency of the brain stem might occur. Duffy and Jacobs,[11] who reviewed 6 cases of thrombosis of the vertebral artery associated with diabetes, hypertension, or other intravascular disease, believed that neither thrombus nor spasm was necessary to cause symptoms but that a drop in the systemic blood pressure itself might be sufficient.

Tatlow and Bammer[44] gave their support to the belief that diminished circulation may occur in one vertebral artery during the normal head movements of daily life because of eccentric rotation of the atlas and the fixed atlantooccipital joint of the opposite side. In postmortem specimens, they were able to demonstrate a marked narrowing of the vertebral artery at the level of the atlas and axis by simple rotation of the head. Grinker and Guy[15] reported the case of a 17-year-old boy who developed thrombosis of the anterior spinal artery following a simple sprain of the cervical spine. These papers have not developed a correlation of the vascular supply with the neuroanatomic structures involved. However, this is attempted in the following case reports.

CASE REPORTS

I. Vascular Insufficiency of Intracranial Distribution of Vertebral Artery Branches

Case 1. A 54-year-old man with moderately severe generalized rheumatoid arthritis was admitted to University Hospital for transurethral resection on April 13, 1958. A general physical examination revealed marked crepitus on any motion of his neck. As a preoperative precaution, a cervical spine roentgenogram was made which revealed an unsuspected atlantoaxial dislocation (Fig. 4). There was "atrophy" of the odontoid process. The transurethral operation was postponed.

The patient and his wife had both noted that he had developed some shortening of his neck within the six months before his admission. During the previous year, he had noticed a progressive tingling and weakness in his upper extremities. He had sustained frequent paroxysms of blurred vision, staggering gait, vertigo, and more or less persistent tinnitus in the left ear. Occasionally, he had had difficulty in swallowing but had not regurgitated food through his nose. There had been no difficulty with the lower extremities. He had had only a diminution in the size and force of his urinary stream without any associated bladder incontinence or loss of bowel control.

On neurologic examination, the only cranial nerve abnormality was diminished left auditory acuity. The patient had generalized weakness in all movements of his upper extremities with impairment more marked in the upper arms and forearms than in the hands. There were no abnormal sensory findings in any modality. His left biceps and triceps, brachioradialis, cremasteric, patellar, and Achilles reflexes were absent. He had no pyramidal tract signs in either the upper or lower extremities.

On April 16, a head halter was applied and 15 lb. of traction was added. The patient had previously been unable to open a cardboard milk container because of profound weakness in his fingers. This impairment in strength had been attributed directly to the severe arthritic changes in the hand. However, within six hours after the initiation of cervical traction, the strength improved markedly in his fingers and he was able to open the same type of container very readily. When the traction apparatus was removed, the patient again developed weakness in the hands and had diplopia. There was a remission of symptoms after Vinke traction was instituted. On April 22, a lumbar puncture was made cautiously and crystal clear spinal fluid removed. The total protein content was 25 mg. per 100 cc. A cystometric examination revealed a normally functioning bladder with some evidence of an outlet obstruction.

On April 27, the patient was operated on by Dr. Robert Bailey of the Bone and Joint Department and Dr. Edgar A. Kahn of the Neurosurgery Department. The suboccipital region was exposed, including C1, C2, and C3 spinous processes and lamina. Reduction of the dislocation and fixation were accomplished by inserting a loop of steel wire about the lamina of the atlas and then placing it about the C2 spinous process. Spinal fusion was then performed, using an autogenous bone graft from the iliac crest. Strength in the patient's hands remains improved. His diplopia has vanished, and his convalescence has been without incident.

Fig. 4. *Case 1.* Lateral view of cervical spine roentgenogram showing the marked atlantoaxial dislocation. Note the anterior cervical fracture-dislocation of the C5 on C6 vertebral body.

Comment. This case is included in a discussion of trauma because it presents the symptoms which may occur with chronic lesions in this region and demonstrates how they may be "turned on and off" by the application and release of cervical traction.

The type of lesion in itself is not unique, but the patient's cerebral symptoms are unusual. Kornblum and co-workers[23] and Stammers and Frazer[40] have reported cases of rheu-

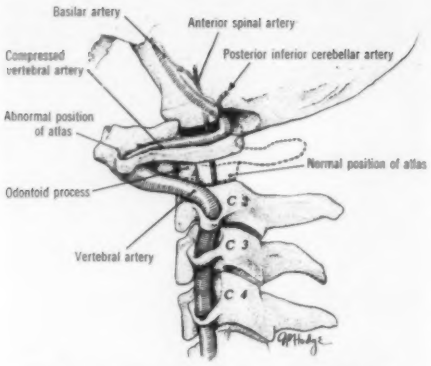

Fig. 5. Lateral view of dislocated atlas on axis showing points of compression of the vertebral artery at [1] the C1 intervertebral foramen and [2] the point where the occipital condyle slides over the groove in the C1 lamina

matoid spondylitis with atlantoaxial dislocation and neurologic symptoms and signs referable to the cervical area. Martin[26] has clearly outlined the pathogenesis of atlantoaxial dislocation which may occur following cervical infection: [1] cervical infection, [2] hyperemia, [3] vertebral decalcification with loosening of ligamentous attachments, and [4] forward slippage of one or both lateral articular facets of the atlas.

With atlantoaxial dislocation, the symptoms might be due to a mechanical cervicomedullary compression locally or partial or complete bilateral occlusion of the vertebral arteries. It is impossible to account for the brain stem symptoms cephalad to the point of dislocation; therefore, the theory of impairment of vascular supply is much more plausible. In addition, the protein of the spinal fluid probably would have been elevated if the symptoms referable to the cervical region were due to chronic spinal cord compression alone.

In cervical spine dislocations, the vertebral arteries may be simultaneously compressed at 3 main sites.

1] Any fracture-dislocation of the cervical spine above the sixth cervical intervertebral foramen may cause compression of these vessels at the displaced intervertebral foramina.

2] Atlantoaxial dislocation will cause compression at the C1 intervertebral foramina (Fig. 5).

3] Atlantoaxial dislocation may cause compression at the point where the occipital condyle slides forward over the well indented groove in the lamina of the first cervical vertebra (Fig. 5).

With bilateral compression of the vertebral arteries, a *relative* vascular insufficiency may occur intracranially in the basilar artery and its branches, as well as cervically in the anterior spinal artery.

With diminished blood flow through the internal auditory artery, vertigo and impairment of hearing may be present.[9,13,32] Hypoxia to the nuclear regions in the brain stem supplied by the pontine arterial branches may result in diplopia.[2] Transient blindness may follow decreased circulation in the posterior cerebral arteries which supply the visual cortex in the occipital lobes.[28,39]

Fig. 6. *Case 2.* Diagram showing the patient in opisthotonos with the arms in extension and hands in ulnar pronation. However, the legs could move readily without any increase in tonus. The latter movement varies from the pattern of "decerebrate rigidity" in which the lower extremities are maintained in extension with markedly increased tonus.

Case 2. A 5-year-old boy was admitted to the hospital on April 16, 1958, after being injured in an automobile accident. He was unconscious but began to respond after thirty minutes. On examination, his vital signs were normal and, although he was semicomatose, he responded to painful stimuli. The legs moved well with a quick withdrawal in flexion and no increased tonus, but the arms responded less readily, going into extension in ulnar pronation simulating a midbrain injury pattern (Fig. 6). His lower extremities moved spontaneously in extension or flexion, but the upper ones only reacted to painful stimuli by rigid extension. Deep reflexes were equal and active, but there were bilateral extensor plantar reflexes. His pupils were equal and small and reacted to light. Left peripheral facial paralysis was found, but the remainder of the cranial nerves were normal. A diagnosis of closed head injury with midbrain contusion or hemorrhage was made. Skull roentgenograms were normal. The initial cervical spine films were technically inadequate due to the patient's movements.

At 4:30 P.M., April 18, the patient, who had been responding by whining and not talking, began to have labored and rapid respirations without retraction of his supraclavicular spaces. His extremities were now limp, and he exhibited only minimal response to pinprick stimuli. The right pupil was larger than the left, but both reacted well to light. The fundi were normal. His extraocular movements showed a right lateral rectus paresis suggesting a sixth nerve palsy. The corneal reflex and facial sensations were intact. Peripheral left facial paresis was present, but his hearing seemed to be intact. He was able to speak but could protrude his tongue only to the level of the lips. His right sternocleidomastoid muscle was strong, but the left was weak. The right upper extremity was notably weakened, but his left upper and lower extremities seemed to be strong. His right intercostal muscles and diaphragm were partially paralyzed. There was hypalgesia to the T4 level on the left and T5 on the right. Deep tendon reflexes were diminished on the right side. He had bilateral extensor plantar reflexes.

At 7:30 P.M., the patient was observed to have further respiratory difficulty, with complete paralysis of his right diaphragm. He was not cyanotic and was conscious and cooperative. Repeat cervical spine films suggested a fracture-dislocation of C2 on C3 vertebra, but subsequent review of them indicated that this was an anatomic variant. No evidence of any pulmonary lesion was seen on the chest film; 3 lb. of cervical traction was applied. Within three minutes, the right intercostal muscles began to function so that the amplitude of the chest excursions returned to normal. Within twelve hours, his cranial nerve signs returned to normal. By 10 P.M., April 19, he had a strong grip in his previously paretic right hand. He was more alert and could be removed from the oxygen tent.

Fig. 7. *Case 2.* The atlantoaxial dislocation is well demonstrated. The odontoid process seems intact, but the transverse ligament has been torn. The arrows indicate the point of displacement at which compression of the cervical spinal cord or vertebral artery may occur.

The patient's skull was too thin for the routine Crutchfield or Vinke skeletal tong traction. On April 21, bur holes were made bilaterally about 6 cm. apart and 2 cm. parasagittally in the frontal and parietal areas. A saw guide was passed between them, and a double No. 20 steel wire was inserted bilaterally in order to maintain traction. A lumbar puncture revealed slightly xanthochromic cerebrospinal fluid. On April 27, a review of the repeat cervical spine films demonstrated a displacement of C1 on C2 vertebra. Attempts at correction in hyperextension had been unsatisfactory due to the hyperactivity of the patient (Fig. 7). Consequently, on April 30, a Minerva jacket was applied and an overhead trapeze attached to the cast to hold the patient's head in hyperextension. This resulted in good cervical spine alignment.

Comment. When this patient was first hospitalized, it was believed that he had had a severe midbrain injury because of the neurologic pattern of the tonic upper extremities with the hands held in ulnar deviation and

pronation. That the lower extremities moved spontaneously without increased tonus should have suggested the error in this diagnosis. The third set of cervical spine films finally demonstrated the atlantoaxial dislocation and suggested the cause of the neurologic deficit. The probable bilateral compression of the vertebral arteries with a gradient of hypoxia in the basilar artery and vascular insufficiency of its branches, the posterior inferior cerebellar arteries, may have resulted in twelfth, tenth, ninth, and eighth cranial nerve impairment. If there was insufficiency to the lateral artery of the medulla, blood flow may have been diminished to the lateral parolivary area with hypoxia to the seventh and sixth cranial nerve nuclei.[2] The vascular supply to these regions of the brain stem varies to some degree, so that a constant clinical picture is not always obtained.

There was a similar gradient of hypoxia in the anterior spinal artery distribution which was responsible for the impaired blood flow through the anterior sulcal artery, resulting in a lessened supply to the hand and arm areas in the lateral corticospinal and rubrotegmentospinal tracts. As a result, there was increased tonus and hyperextension of the arms with the hands in ulnar deviation. In contrast, the preserved blood supply to the leg area of the lateral corticospinal tract via the posterior spinal and funicular arteries and the more posterior portions of the arteriae coronae permitted flexion movement of the lower extremities without increased tonus (Fig. 3).

A certain amount of depletion of the blood supply through the anterior sulcal arteries and secondarily through the more anterior portions of the arteriae coronae occurred, so that the peripheral arterial branches to the lateral spinothalamic tract carried less blood; that part of the spinal cord may have been damaged. This could have resulted in a transient or permanent loss of pain and temperature sensation. The latter could not be tested in this child due to impaired state of consciousness.

The paralysis of the right diaphragm was no doubt due to a direct compression to the upper right cervical nerve roots at the site of the dislocation. Before seeing the spine roentgenograms, one of the examiners had considered the possibility of a right pneumothorax when the chest did not expand properly. He had not suspected the possibility of a cervical fracture-dislocation.

The rather abrupt conversion of a seriously ill patient to a fairly comfortable one a short time after cervical traction was instituted was interesting to observe. This could not be attributed to high cervical spinal cord compression alone but had to be in combination with a compromise of the blood supply to the brain stem and cervical spinal cord.

Case 3. A 21-year-old housewife was thrown through the shatterproof windshield of a car traveling at 65 miles an hour when the vehicle struck a bridge abutment. She lost consciousness immediately and was in that state an hour and a half later when examined by Dr. Richard Smith at University Hospital. Her blood pressure was 100/70; pulse, 82 per minute; and respirations, 16 per minute. She had a 7-cm. laceration in the right parietotemporal area extending down to the calvarium, with an associated avulsion of the superior portion of the right ear. She had a massive contusion abrasion which included the right side of the face and neck. The right internal carotid artery pulsation could be palpated. She had anisocoria, with the right pupil about three-fourths dilated compared to the small left pupil; both were fixed to light. There were no hemorrhages or papilledema. The extremities were all flaccid, but painful stimuli caused weak movement of the left arm and leg; the right extremities remained paralyzed. There was good functioning of the intercostal muscles bilaterally. Upon checking pinprick sensation, the examiner observed a painful response above the level of C4 dermatome. Below this, he noted that the patient had a response but only as a result of multiple pinpricks at the same location creating a summation effect. She had complete bilateral upper extremity areflexia. The right patellar reflex was absent, but the left patellar and Achilles reflexes were present. There were bilateral extensor plantar reflexes.

Skull roentgenograms and cervical spine films in flexion, neutral, and hyperextension positions showed no evidence of fracture or dislocation. It was thought that hyperextension of the cervical spine might demonstrate some displacement not otherwise visible.

Immediately after admission, the patient was taken to the operating room because of a tentorial pressure cone which was manifested by a dilated right pupil and bilateral extensor plantar reflexes. Trephine openings were made bilaterally at the frontal, temporal, and posterior parietal regions. Hemorrhage or contusion was not apparent, but, because of the presence of moderate cerebral edema, a right subtemporal decompression was made.

Twelve hours postoperatively, the dilated right pupil was smaller in size than preoperatively, although some degree of anisocoria persisted. The

patient was comatose, and only a sensory level to pinprick could be demonstrated at the C4 dermatome. She was totally areflexic and had no extensor plantar reflexes. Painful stimuli elicited no movement except for an increase in respiratory rate upon pinprick. Her respirations were carried out by both the intercostal muscles and the diaphragms. Since she had developed slight hypotension, 80/64, she was started on Solu-Cortef intravenously.

Thirty-six hours after operation, the only change in her condition was response to pinprick over the entire body. The lower extremities moved on painful stimuli produced by supraorbital pressure or by local withdrawal on pinprick. The deep reflexes in the lower extremities and the extensor plantar reflexes had returned. A tracheotomy was performed, and her condition improved even more.

Comment. Since this patient had definite signs of a tentorial pressure cone, trephination for a possible intracranial hemorrhage was essential. As has been indicated, only moderate cerebral edema was found. In the literature, attention has been called to the importance of suspecting the presence of a traumatic internal carotid artery thrombosis in cases of craniocerebral trauma whenever a severe contusion is noted in the cervical area.[36] However, little mention is made of a possible traumatic spasm or thrombosis of the vertebral arteries in such cases. Such a type of lesion could have been present in this patient.

Fracture-dislocation of the cervical spine, which was excluded by roentgenogram, and a severe spinal cord contusion were considered because of the patient's partial C4 dermatome sensory level to pinprick stimulus. If either of these lesions had been present, complete areflexic tetraplegia with a sensory level to C4 dermatome and paralysis of the intercostal musculature probably would have been present. Instead, there were intercostal muscle respirations, the definite sensory level above C4 but the peculiar summation effect to pinprick below C4 dermatome, and lower extremity reflexes indicating an incomplete lesion.

A spasm or thrombosis of the vertebral arteries was suspected. The region of the thoracic cord from T4 segment through the T12 segment is supplied by vessels which arise from the aorta and most frequently enter at one of the intervertebral foramina between T8 and L4 vertebrae. They are pictured as entering at T9 intervertebral foramen (Fig. 2). The blood flow, in both cephalad and caudad directions, was adequate, so that there was no hypoxia to the neural segments supplying the intercostal musculature. These muscles, therefore, remained functional.

The phenomenon, described in the original examination, of a definite sensory level at C4 with an immediate response to pinprick above that point suggested that the blood supply from the anterior spinal artery was competent above that level. Below the C4 dermatome, multiple painful stimuli were required to achieve a response. This indicated that the lateral spinothalamic tract was suffering from some hypoxia within the anterior sulcal artery but, even more, from a diminished blood flow through the ventral portions of the arteriae coronae which supply the anterolateral periphery of the cord (Fig. 3). That this bizarre sensory pattern disappeared within thirty-six hours suggested that these arteries again carried their normal amount of blood and the periphery of the spinal cord was reoxygenated.

As has been indicated in the previous case, the hypoxia gradient in the anterior spinal and thus the anterior sulcal arteries resulted in impairment in the fibers of the medial portion of the cervical lateral corticospinal tract, so that the hand and arm motor fibers became most impaired. As a result, there was a complete paralysis of the upper extremities. The outer fibers, or lower extremity component, of the lateral corticospinal tract are supplied by the posterior funicular or radicular branches of the paired posterior spinal arteries. The slighter degree of vascular insufficiency to these was evident, since lower extremity deep reflexes were preserved and a withdrawal response to painful stimulus could be elicited in both feet and legs within twenty-four hours.

The patient was scheduled for vertebral arteriography, but the procedure was cancelled for fear the transient hypoxia caused by the arterial injection might be sufficient to increase her neurologic difficulty.

II. Vascular Insufficiency of the Cervical Distribution of the Anterior Spinal Artery

Case 4. A 49-year-old man, who had suffered from arthritis of the cervical spine for ten years, went to bed after drinking a large quantity of beer. A few hours later, after arising from bed, he fell down a full flight of stairs. Upon regaining consciousness a few minutes later, he could

Figure 8

Fig. 8. *Case 4.* Lateral view of the C4-C5 fracture-dislocation site of hypertrophic arthritic spine (retouched). (Reprinted from Schneider, R. C., Cherry, G., and Pantek, H.[37])

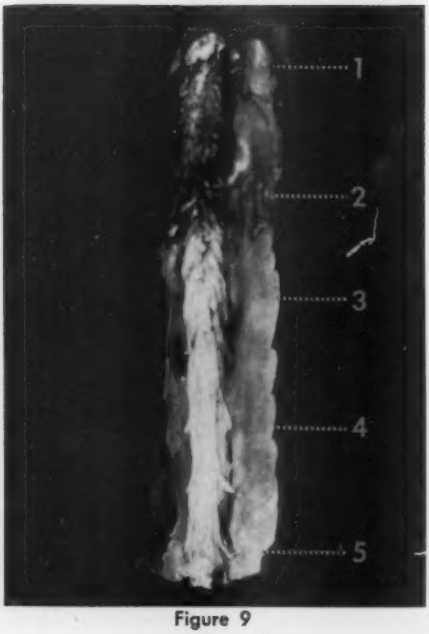

Figure 9

Fig. 9. *Case 4.* Autopsy specimen shows the zone of acute compression and destruction of the cord. The more caudal portions of the spinal cord appeared grossly normal. Sections taken at the numbered levels are shown in Figure 10. (Reprinted from Schneider, R. C., Cherry, G., and Pantek, H.[37])

Fig. 10. *Case 4.* Cross sections of the specimen show an initial zone of almost complete destruction. A segment cephalad[1] and 2 segments more caudally[3,4] show a relatively less destroyed segment, but further distally, 6 segments below the site of injury, is a zone of central infarction or necrosis. (Reprinted from Schneider, R. C., Cherry, G., and Pantek, H.[37])

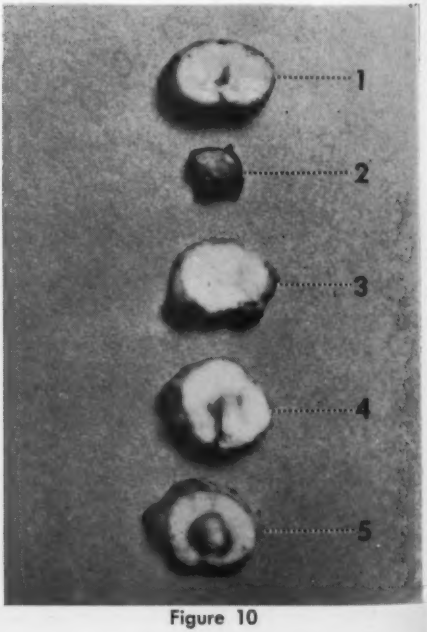

Figure 10

move only his upper arms slightly and, shortly thereafter, became completely paralyzed in all 4 extremities.

The patient was transferred to University Hospital, where he was found to be well oriented and cooperative. His head was rigidly locked in hyperextension, so that the head remained elevated several inches above the table even after all support had been withdrawn. Palpation posteriorly over the cervical spine revealed marked tenderness at the C4 spinous process. All sensory modalities were lost to the C4 dermatome on the right and C5 on the left. All 4 extremities were completely paralyzed. The right triceps and radioperiosteal reflexes were intact, but otherwise there was a complete areflexia with no pathologic reflexes.

Roentgenograms of the cervical spine showed pronounced comminution and fracture-dislocation of C4 vertebral body anteriorly on the C5 vertebra (Fig. 8).

Crutchfield's skeletal tong traction was applied after the patient was placed on a Stryker frame. The intercostal muscles had been paralyzed immediately, and the diaphragmatic respirations had gradually become more labored. The patient died three days after his fall.

Autopsy disclosed a severe crushing destruction of the cervical cord immediately at the site of the fracture-dislocation (Fig. 9), with central cord destruction several segments above and below the site of injury; the lowermost point of destruction was fully 6 neural segments below the site of constriction of the cord (Fig. 10).

Comment. This report was originally published elsewhere to demonstrate a case of acute central cervical spinal cord injury.[37]

It had been impossible to explain the peculiar phenomenon of a point of destruction at C4-C5 interspace followed by relatively less damaged caudal sections of the cord, only to find a much more marked area of central destruction some 6 neural segments distal to the site of injury. In a comprehensive piece of work, Zülch[49] has demonstrated the reason for this. He has shown the general vascular supply to the spinal cord and the direction of blood flow and indicated 2 zones of "poor or almost compromised collateral circulation" in the anterior portion of the cord at T4 and L1 segments, respectively (Fig. 2).

Again the problem is present of diminution of blood flow in the anterior spinal arteries due to bilateral spasm or thrombosis of the vertebral arteries in the intervertebral foramina at the C4-C5 fracture-dislocation site rather than at the atlantoaxial junction as described in Cases 1 and 2. In this patient, a gradient of hypoxia proceeded in a caudal direction rather than cephalad into the intracranial branches of the vertebral artery, as occurred in Cases 1, 2, and 3. There was no thrombosis of the anterior spinal artery but instead a gradual diminution in blood supply as the critical zone at T4 was approached, so that a zone of central infarction occurred. Max Schneider[35] has drawn the analogy of a reservoir with a system of irrigation ditches. If there is a diminution of the amount of water in the system, the ditches which supply the fields or meadows farthest from the source of the water supply suffer the most because of the gradient of depletion in the amount of water.

III. Vascular Insufficiency of the Anterior Medial Spinal (Thoracic Anterior Spinal) Artery

Case 5. A 38-year-old mechanic was sitting on the ground beneath a truck when the power tail gate fell on his back. The patient had an immediate, complete areflexic paraplegia with an absolute sensory level at T5 on the left side and T6 on the right. An hour later, the level was recorded as being at T7 on the left side and T8 on the right. A roentgenogram of the thoracolumbar spine revealed a fracture-dislocation at T11-T12 interspace with marked destruction of the T12 vertebra (Fig. 11). There was no demonstrable bony abnormality above this site. He was transferred to University Hospital three hours later, where the above findings were noted and a lumbar puncture was done. A grossly bloody cerebrospinal fluid was obtained, and, on myelography, a dural tear was demonstrated at T12-L1 interspace with some extravasation of Pantopaque into the paraspinous regions (Fig. 12). Nevertheless, some dye ascended in the spinal canal to the T9-T10 vertebral level before an almost complete block occurred. A small amount of the Pantopaque trickled up the right lateral gutter of the spinal canal above this level to T5 vertebra.

An exploratory laminectomy was performed the same day. Massive disruption of the interspinous ligament between T11 and T12 vertebrae was found, with avulsion of the muscles from the bone. Upon retraction of the paraspinous musculature, the lacerated dura was visualized. The left inferior T11 facet was found lying free in the wound and was removed. The right T11 lamina was removed and the dura explored. Several dural lacerations were demonstrated which could not be closed. Leakage of cerebrospinal fluid into the wound might have prevented "take" of any bony spinal fusion. To prevent successfully the leak, a dural graft would have been necessary, but this would have required sacrificing considerably more bone to reach the edges of the dural margin. After

some consultation, Dr. T. R. Lamot, the orthopedic surgeon, elected to denude the right inferior T11 facet and superior T12 facet of cartilage and wire them together. The patient's back was hyperextended. Then, 2 more wires were passed around the T10 and T11 vertebral spinous processes and the T9 and T12 vertebral processes. Postoperatively, the patient's sensory level dropped to T7 on the left and T10 on the right. The wounds were closed. The patient's convalescence was uneventful.

Fig. 11. *Case 5.* Lateral roentgenogram shows severe compression fracture-dislocation at T11-T12 level with marked kyphos. No bony abnormality at a higher level in the thoracic spine is seen.

Comment. This patient demonstrated that, with severe anatomic disruption of the thoracic spinal cord at T11-T12 interspace, there may be a considerably higher level of physiologic interruption at the vicinity of T6 level due to vascular insufficiency to the midthoracic cord. As has been indicated above, the major blood supply to the thoracic cord is from the aorta by the great ventral radicular spinal artery, entering somewhere between the T8 to L4 segments (Figs. 2 and 3) to proceed cephalad and caudad along the anterior surface of the thoracic cord. Since there is a zone of poor collateral circulation at the T4 segment between the cervical anterior spinal artery and the anterior median spinal or thoracic anterior spinal artery, there is no caudal blood flow from the cervical region. Thus, when the anterior medial spinal or thoracic anterior spinal artery was occluded at the site of injury, there was a gradient of hypoxia with swelling of the thoracic spinal cord at the T6 level. This accounts for the unusual sensory level well above the site of the lesion and the peculiar myelographic findings.

DISCUSSION

After a diagnosis of vascular insufficiency is made, the question arises as to whether there is any effective therapy which may be used. The prompt application of cervical traction is the best method of relieving pressure on the vertebral arteries. Certainly, in acute lesions with more spasm of the vertebral artery, early decompression of the intervertebral foramina might do more harm than good. A primary requisite is that the patient have a good airway in order to avoid hypoxia. An early tracheotomy, therefore, may be advisable in high cervical dislocation cases. Schmidt[34] and Johnson[19] have advocated the use of 6% carbon dioxide inhalations as a method of dilating the cerebral vessels and thus getting more oxygen to the brain. There is considerable doubt as to whether this method is of much practical value. Bilateral stellate ganglion blocks might be considered, but, if through an error in technic the local anesthetic should spread upward to involve the C3, C4, or C5 nerve roots, one diaphragmatic leaf might be

paralyzed. If the needle happened to penetrate the pleura and cause a pneumothorax, the factors causing hypoxia would increase and perhaps create further neurologic disability.

PROJECTED STUDY

Radner[30] has described the partial occlusion of the vertebral artery by cervical osteophytes. Bartschi-Rochaix[5] has mentioned the part played by osteophytes in compressing the vertebral artery in "cervical migraine." Brain and Wilkinson[8] have noted the more than coincidental relationship between cervical hypertrophic spurs and syringomyelia. Schneider and associates[37,38] have described the syndrome of acute central cervical spinal cord injury in patients with hypertrophic arthritic spines who had sustained hyperextension trauma to the spine. It is gradually becoming more apparent that the osteophytes may cause impingement upon the vertebral arteries in the intervertebral foramina and may be responsible for a chronic or an acute central hypoxic gradient in the cervical anterior spinal artery resulting in a syringomyelic lesion.

For these reasons, the project of vertebral arteriography is being embarked upon in this clinic in most patients with fracture-dislocations of the cervical spine and in all patients with syringomyelia to determine whether more information can be obtained with regard to diagnosis, etiology, and treatment of these conditions.

SUMMARY

In the study of the relationship of trauma to the acute and chronic damage to the brain stem and spinal cord, some clinicopathologic effects are not readily explicable on the basis of the trauma at its primary site. Often, a remote effect occurs which is due to a vascular insufficiency of the brain stem or the spinal cord.

The normal circulation of the brain stem and spinal cord has been reviewed.

To demonstrate the problems, 5 cases were presented. In 3 patients, there was vascular insufficiency of the brain stem; in 1, of the cervical cord; and, in the fifth, impairment of blood supply to the thoracic spinal cord.

A plea is made for a more adequate clinicopathologic examination of the cervicomedullary region and its functions. It is believed that some traumatic craniocerebral deaths for which no cause of death can be found intracranially may have a vertebral vascular insufficiency of the brain stem and cervical spinal cord.

The relationship between vertebral arterial compression by cervical fracture-dislocations and by hypertrophic cervical osteophytes with neurologic lesions such as syringomyelia has been suggested. A projected study with vertebral arteriography of patients with these lesions has been advocated.

Fig. 12. *Case 5.* Myelogram shows partial block at the T9-T10 vertebral level. At the T11-T12 interspace is a deformity in the Pantopaque column caused by the T12 right superior articular facet's (arrow) being dislocated into the center of the spinal canal. At this level, a meningeal tear with extravasation of Pantopaqe into the left paraspinous tissues is present.

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Motor unit territory and muscle fiber concentration in paresis due to peripheral nerve injury and anterior horn cell involvement

Francesco Erminio, M.D., Fritz Buchthal, M.D., and Poul Rosenfalck, M.Sc.

HISTOLOGIC studies show that muscular atrophy caused by involvement of the lower motor neuron is associated with loss of some motor units and changes in the composition of surviving motor units. These changes appear, on the one hand, as the patchy muscular atrophy associated with partial denervation[1–3] and, on the other hand, as reinnervation of denervated muscle fibers through branching of the nerve fibers which supply the surviving motor units.[4–6] A quantitative estimate of these changes is, however, not easily made with histologic methods.

In normal muscle, the area over which the fibers of the individual motor unit are distributed was delineated by means of multilead recording of the action potentials from the motor unit.[7,8] That the motor units defined anatomically and electrophysiologically are identical was thereby demonstrated.

Previous electromyographic studies in paresis secondary to involvement of the anterior horn cells have disclosed action potentials which were synchronous over a large part of the muscle cross section.[9–13] This could be due either to an enlargement of the surviving motor units or to a forced simultaneous discharge of several anterior horn cells. The latter possibility would imply that, under these conditions, the electrophysiologically defined motor unit consisted of more than one anatomic motor unit.

The aim of the investigation presented here is to determine the changes in motor unit organization associated with neurogenic paresis.

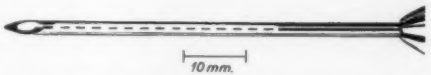

Fig. 1. Multilead electrode containing 14 platinum leads 1.5 mm. in length. Distance between centers of adjacent leads, 2.5 mm. Diameter of needle, 1 mm.

Data are given for motor unit territory and maximum voltage in paresis caused by traumatic lesions of the peripheral nerve and in atrophy secondary to involvement of the anterior horn cells.

METHOD

Electrical activity in different parts of the muscle cross section was recorded by means of a multilead electrode.[7] This contained 12 or 14 leads spaced over 24 or 35 mm. along the needle, which had a diameter of 1 mm. (Fig. 1). The distance between the centers of the adjacent platinum leads was 2 or 2.5 mm., and each lead had an extent of 1.5 mm. The territory of the motor unit was mapped by switching the single leads of the electrode successively to 2 channels of the electromyograph, while a third channel was kept in constant connection with one of the central leads recording an action potential of high voltage.

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The potentials were recorded between the different leads of the multielectrode, with one of its outer leads as the indifferent electrode situated in a portion of the muscle where no potentials were recorded. The possible influence of the indifferent electrode and details of the recording technic have been described previously.[7,8] Whenever possible, at least 6 different motor units were scanned in each muscle. These could be obtained by 3 or 4 insertions of the electrode transverse to the fiber direction.

The potentials were recorded at slight to moderate voluntary effort in slightly paretic muscles and at strong effort in severely paretic muscles. The patient was instructed to maintain constant effort during the scanning of the motor units.

The basis for determining the territory occupied by the fibers of a motor unit from the action potential distribution is the finding that, whenever a potential is recorded containing fast positive-negative components of a duration of less than 0.2 msec. ("spikes"), the muscle fibers which give rise to these potentials are situated at a distance of less than 1 mm. from the recording lead.[14] Spikes occur in the potentials when the voltage exceeds a certain level denoted as *spike level*. The potentials of lower amplitude without spikes are volume-conducted from fibers at larger distance. The *motor unit territory* was obtained from a plot of the voltage variation along the multielectrode as the stretch over which potentials containing spikes are recorded. The *maximum voltage* recorded along the multielectrode is a gauge of the number of muscle fibers per unit area belonging to the motor unit under investigation. This is denoted as fiber concentration.[8]

In addition to the mapping of the motor units, the electromyographic pattern was recorded at maximum effort, the average action potential duration was measured as obtained in random insertions of concentric electrodes, and the muscle was searched for the presence of fibrillation potentials. Findings with respect to these data were classified according to Buchthal.[15]

Muscle force was estimated for each muscle by 2 examiners and graded according to the scale suggested by the Medical Research Council.[16]

PATIENTS

Motor unit territory and maximum voltage were studied in 63 patients with neurogenic paresis. In 28, paresis was caused by peripheral nerve injury. In 27, paresis was secondary to involvement of the anterior horn cells. Furthermore, 4 patients with peroneal muscular atrophy (Charcot-Marie-Tooth) and 4 with muscular atrophy associated with syringomyelia were studied. Finally, to evaluate the effect of spasticity, 3 patients with spasticity due to cerebral thrombosis without involvement of the lower motor neuron were studied.

Paresis secondary to peripheral nerve injury. The 28 patients, 24 males and 4 females, were between 13 and 73 years of age, half of them between 18 and 30 years old. In 20 patients, paresis was caused by damage to the brachial plexus, either involving all 3 trunks or the upper trunk only (Duchenne-Erb). In 5 patients, there was a partial interruption of the axillary nerve and, in 3, a partial interruption of the radial nerve. The paresis had lasted for less than one year in 17 and for more than one year in 11 patients. In 4 patients, the study of a given muscle was repeated ten months later, and, in 7, two muscles were examined. In all, 40 muscles were investigated (14 brachial biceps, 18 deltoid, and 8 extensor digitorum communis).

In 28 muscles, paresis was severe (force graded as 3 or less[16]); in 12 muscles, paresis was moderate (force graded as 3$^+$ or more). Fibrillation potentials were present in 34 of the 40 muscles investigated. Signs of a substantial loss of motor units at maximum effort were found in almost all muscles investigated. The mean action potential duration was increased in most of the muscles examined eight months or more after the injury; the incidence of polyphasic potentials with short spike duration had increased in two-thirds of these muscles, indicating reinnervation.

Paresis secondary to involvement of the anterior horn cells. A group of 26 patients (21 males and 5 females) who suffered from amyotrophic lateral sclerosis was examined; 24 of these were between 40 and 70 years of age. In addition, a 13-year-old girl with spinal muscular atrophy was examined. The patients had all been hospitalized on a neurologic service, and the diagnosis of amyotrophic lateral scler-

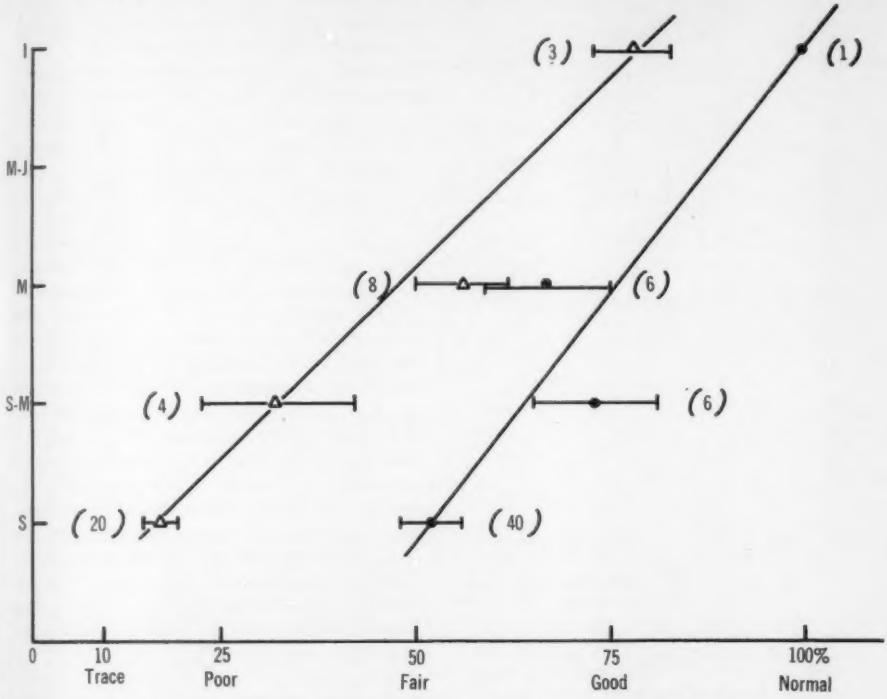

Fig. 2. This shows that a given electromyographic pattern is associated with a higher degree of paresis in peripheral nerve injury (△) than in amyotrophic lateral sclerosis (●) *Ordinate:* Electromyographic pattern at maximum effort; S = single oscillations, M = mixed pattern, I = interference (for definition see [15]). *Abscissa:* Force grading according to the scale suggested by M.R.C.[16] The figures in brackets denote the number of muscles, and the horizontal bars indicate the standard error of the mean.

osis was well established. In all, the muscular paresis and atrophy were progressive; there were fasciculations, spasticity in some, lack of deep reflexes in other muscles, and lack of sensory involvement. The paresis had lasted for less than one year in 4 and for more than one year in 22 patients. In 13 patients, more than one muscle was studied. In all, 56 muscles were investigated (30 brachial biceps, 19 anterior tibial, and 7 femoral rectus); 15 of these 56 muscles displayed a pronounced degree of spasticity in addition to atrophy.

In 21 muscles, the paresis was severe (force graded as 3⁻ or less); in 27, moderate (force graded as 3 to 4⁺); and in 8 muscles, slight or with no reduction in force (force graded as 5 or 5⁻). Fibrillation potentials were present in 5 of 16 muscles with mild degree of involvement and in 27 of 37 severely involved muscles. The average action potential duration was increased, as was the incidence of polyphasic potentials in one-fourth of the muscles investigated. The correlation between force grading and the electromyographic pattern at maximum effort is given in Figure 2. It is worth noticing that the average force of muscles showing single oscillations (S) was as much as half that of normal muscle, while, in paresis of peripheral neurogenic origin, it was only 15% of normal maximum force. This is reflected in the finding that 11 of 40 muscles with single oscillations at maximum effort were graded as 4 ("good") or more. Therefore, muscles were classified into 2 groups accord-

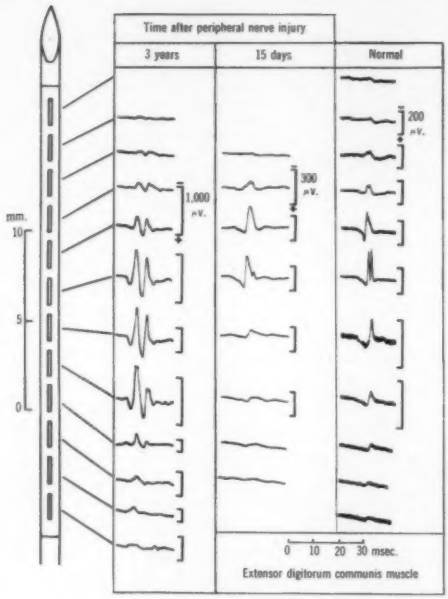

Fig. 3. This shows the higher voltage and the spread of potentials from a motor unit over more leads of the multielectrode than in normal muscle in paresis caused by peripheral nerve injury examined more than eight months after the lesion (m. extensor digitorum communis).
Column 1: Patient G.R.L.; force graded as 4⁻; damage to brachial plexus occurred three years before the examination.
Column 2: Patient G.H.L.; force graded as 1; damage to radial nerve occurred fifteen days before the examination.
Column 3: Normal muscle

ing to the electromyographic pattern at maximum effort, 1 comprising muscles showing single oscillations ("severely involved") and 1 with mixed pattern or interference ("slightly involved").

Patients with peroneal muscular atrophy and syringomyelia. In the 4 patients with peroneal muscular atrophy, 5 anterior tibial muscles were investigated, all severely paretic (force graded as 3 or less). At electromyographic study, there were single oscillations in all and fibrillation potentials in 2 of the muscles examined. In the 4 patients with syringomyelia, 4 brachial biceps were studied; these had a moderate degree of paresis (force graded as 3⁺ to 4), and 3 had fibrillation potentials.

Spastic muscles from patients with cerebral thromboses. In this group, 2 anterior tibial and 1 brachial biceps muscle were studied. These displayed a high degree of spasticity. There were no fibrillation potentials.

RESULTS

1. *Paresis secondary to peripheral nerve injury.* Approximately ten months after damage to a peripheral motor nerve, the maximum voltage and the territory of the motor units were found to be increased. Examples of multielectrode recordings in paresis due to peripheral nerve injury are shown in Figure 3. The first column represents the distribution of the action potentials of a motor unit over the cross section of m. extensor digitorum communis in a patient with a nerve lesion incurred three years before examination. Spike potentials were of higher voltage and spread over a larger number of leads than in the case illustrated in column 2, where only fifteen days had elapsed after the injury. Column 3 illustrates the distribution of potentials in a motor unit from normal muscle.

The paretic muscles investigated fell into 2 groups: those examined within three months after injury to the nerve and those examined more than eight months after injury. The average voltage variation of motor unit potentials for these 2 groups of muscles over the cross section of 3 different muscles (brachial biceps, deltoid, and extensor digitorum communis) is given in Figure 4. In paretic muscles examined eight months or longer after nerve injury, the action potential voltage as recorded on the different leads of the multielectrode was significantly higher than in normal muscle. The motor unit territory, on the other hand, was not increased to the degree to be expected from the increase in voltage. This is due to the fact that the voltage level (spike level) at which the territory was measured was also substantially higher than in normal muscle.

Average values of maximum voltage and territory are listed in Table 1. With a nerve injury incurred eight months or longer before the investigation, the maximum voltage of the motor unit potentials was 2.4 to 3.5 times that of normal muscle. The extent of the

motor unit territory, determined as the region over which spike potentials were recorded, was increased by 40% in the brachial biceps and the extensor digitorum communis and by 15% in the deltoid. In muscles in which motor nerve supply was damaged less than three months before, maximum voltage was 1.8 times the normal in the deltoid and unaltered in the brachial biceps and the extensor digitorum communis. The motor unit territory was within the limits of normal muscle.

The variation in maximum voltage and territory for different motor units of muscles investigated more than eight months after nerve injury is given in Figure 5. The variation within the same muscle and within different types of muscle was the same as in normal muscle. Similarly, the maximum voltage found within a motor unit increased with increasing territory, as was found in normal muscle.[8]

The changes in maximum voltage and motor unit territory did not correlate with the degree of paresis as determined by muscle grading. Thus, in 10 muscles of the group in which paresis had lasted more than eight months and in which the paresis was slight (force graded as 3+ or more), maximum voltage within the motor unit and territory did not deviate significantly from values found in 15 muscles which still had a severe paresis (force graded as 3 or less).

In paretic muscles examined more than eight months after a nerve injury, the number of motor units which could be discriminated by their action potentials recorded at a given lead of the multielectrode was reduced as compared with the number picked up in normal muscle. Even with relatively strong effort, potentials from only 3 motor units could be identified as compared with 6 in normal muscle.

Paresis secondary to involvement of the anterior horn cells. Typical examples of multilead scanning of motor units from 4 patients with amyotrophic lateral sclerosis are given in Figure 6. The first 2 columns represent recordings from severely paretic muscles (single motor unit potentials at maximum effort, force graded as 1 to 3); the potentials illustrated in columns 3 and 4 were led off in less involved muscles. As compared with potentials in motor units from normal muscle (column 5), poten-

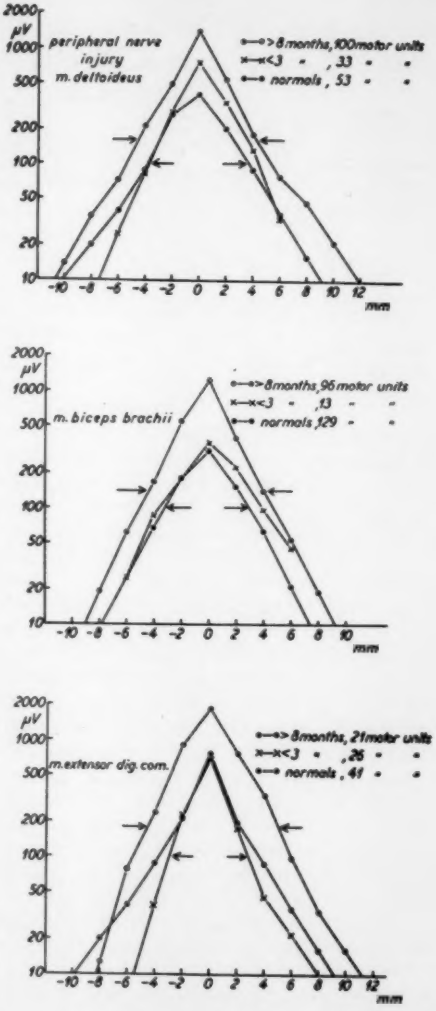

Fig. 4. Voltage variation over motor units of muscles paretic from peripheral nerve injury (m. deltoideus, m. biceps brachii, and m. extensor digitorum communis). O——O injury more than eight months before examination. X——X injury less than three months before examination. ●——● normal muscles. The arrows indicate the spike level. *Ordinate:* Voltage in μv. (logarithmic scale). *Abscissa:* Distance along the multilead electrode measured from the lead which recorded the potential of maximum voltage.

TABLE 1
MOTOR UNIT TERRITORY AND MAXIMUM VOLTAGE IN PERIPHERAL NERVE LESIONS AS COMPARED WITH NORMAL MUSCLE

Muscle	Number of patients or subjects	Number of motor units	Spike level in μv.	Territory in mm. Mean value	Territory in mm. Standard deviation	Maximum voltage in μv. Mean value	Maximum voltage in μv. Standard deviation
Nerve lesion more than eight months before examination							
Biceps brachii	11	100	150	7.3 ± 0.3	2.7	1,300 ± 100	1,040
Deltoideus	11	103	160	7.8 ± 0.3	3.1	1,400 ± 100	1,030
Extensor digit. communis	3	23	180	8.0 ± 0.5	2.2	1,900 ± 170	780
Nerve lesion less than three months before examination							
Biceps brachii	3	13	100	7.3 ± 0.5	1.8	390 ± 40	150
Deltoideus	7	34	110	7.2 ± 0.6	3.3	830 ± 60	380
Extensor digit. communis	5	26	100	5.3 ± 0.3	1.6	720 ± 40	180
Normal subjects							
Biceps brachii	24	129	100	5.1 ± 0.2	2.4	370 ± 20	190
Deltoideus	7	52	100	6.7 ± 0.4	3.0	450 ± 30	190
Extensor digit. communis	11	43	100	5.5 ± 0.3	2.1	800 ± 60	390

tials in severely involved muscles were picked up by a larger number of leads and had a considerably higher voltage. The average voltage variation along the multielectrode in severely and slightly involved brachial biceps and anterior tibial muscles is given in Figure 7. There was a striking increase in voltage, the maximum voltage within the motor units being 5 to 8 times that of normal muscle. The extent of the territory covered by the fibers of the individual motor units in the severely involved muscles was 80 to 140% larger than in normal muscles. Although this is a substantial increase, the extent of the territory is not increased to the degree that might be expected from the increase in voltage. As in paresis secondary to peripheral nerve injury, this is due to an increase in the voltage level (spike level) at which the territory was measured.

Average values of motor unit territory and maximum voltage in different muscles are listed in Table 2. The increase in territory and maximum voltage exceeded by far that of equally paretic muscles in peripheral nerve injuries (Table 1). The same was the case in a severely involved brachial biceps from a patient with spinal muscular atrophy (Werdnig-Hoffmann). The motor unit territory amounted to 16.2 mm. (average from 12 motor units), and the maximum voltage was 3 mv., 9 times that of normal motor units.

As in normal muscle, territory and maximum voltage were correlated: the larger the territory of a motor unit, the higher its maximum voltage. But the voltage which corresponded to a given territory was much higher in paretic than in normal muscle.

The variation in maximum voltage and territory of different motor units in the brachial biceps of the 11 patients with severe amyotrophic lateral sclerosis are given in Figure 8. As compared with the distribution in normal muscle, maximum voltage showed a 5-times greater range. Thus, a considerable fraction of the motor units had maximum voltages never found in normal muscles. On the other hand, the variation in territory was the same as that of normal muscle in spite of the increase in mean value. This reflects the loss of motor units with an extent smaller than 4 mm. and the occurrence of motor units with territories larger than those present in normal muscles. The loss of some of the motor units and the increase in territory of the surviving motor units is apparent also from the reduction in the number of different motor units which could be discriminated by their action potentials on a single lead of the multielectrode. In severely involved muscles, only 2 or 3 different motor unit potentials were recorded as compared to 6 in normal muscle.

Findings in less involved muscles (force graded as 4 or more and with "mixed pattern" in action potential recordings at maximum effort) were in between the values obtained in severely involved muscles and normal muscles

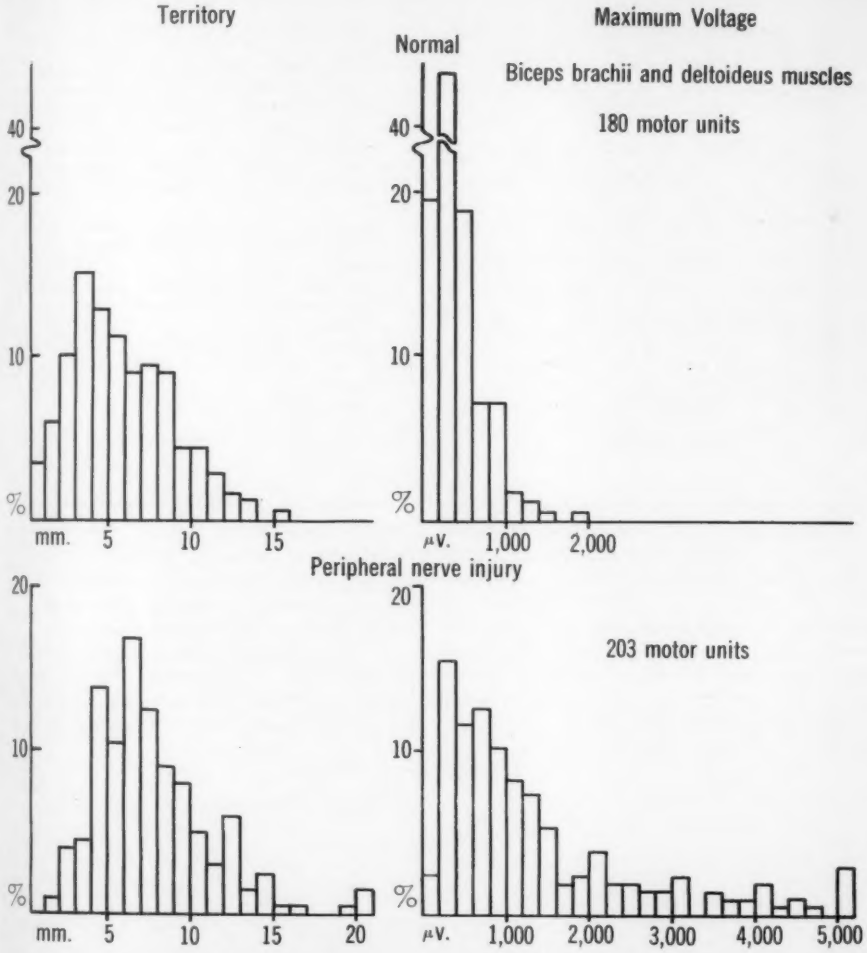

Fig. 5. Histograms of motor unit territory and maximum voltage in paresis due to peripheral nerve injury investigated more than eight months after the injury (below). For comparison, histograms are given for normal muscle (above). *Abscissa:* Ranges of territory and maximum voltage. *Ordinate:* Percentage of motor units in each range.

(Fig. 6, Table 2). The group of slightly involved muscles is somewhat heterogeneous, containing, in addition to slightly paretic muscles, 4 muscles without appreciable paresis or atrophy and with only a slight degree of spasticity. The maximum voltage in these muscles was increased by about 3 times, and the extent of the motor unit territory was 40 to 130% higher than that of normal muscle (12 motor units).

Whether spasticity as such gives rise to changes in maximum voltage and average territory was investigated in 2 ways: comparing severely involved muscles with and without

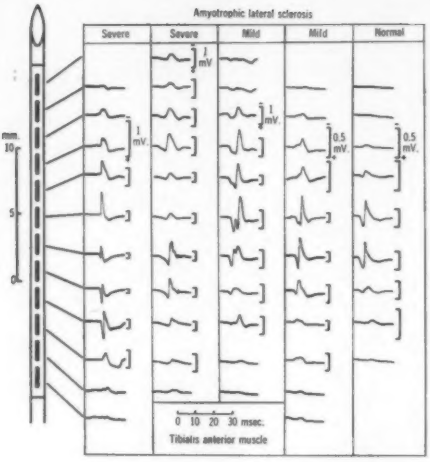

Fig. 6. Figure shows the spread of potentials of a motor unit over more leads of the multielectrode and higher voltage than in normal muscle in paresis due to amyotrophic lateral sclerosis (m. tibialis anterior). *Column 1:* Patient S.S.; force graded as 3⁺; onset of disease four years before examination.
Column 2: Patient H.V.E.L.; force graded as 3; onset of disease six years before examination.
Column 3: Patient H.V.E.L.; force graded as 4; onset of disease six years before examination.
Column 4: Patient M.H.N.; force graded as 5⁻; onset of disease four months before examination.
Column 5: Normal muscle

signs of spasticity, the former had a smaller increase in motor unit territory than did equally paretic muscles without spasticity, while the increase in maximum voltage was the same in both groups (Table 3). Furthermore, in muscles in which spasticity was caused by cerebral thrombosis without direct affection of the lower motor neuron, there was no change in maximum voltage or in motor unit territory as compared to normal muscle.

Findings in peroneal muscular atrophy (type Charcot-Marie-Tooth) and in syringomyelia. In 4 cases of peroneal muscular atrophy, 5 severely paretic muscles showed significant increases in maximum voltage, spike level, and extent of motor unit territory (Table 4).

In 4 moderately paretic muscles from 4 patients with syringomyelia, the maximum voltage was 3 times that of normal muscle and the extent of motor unit territory was normal.

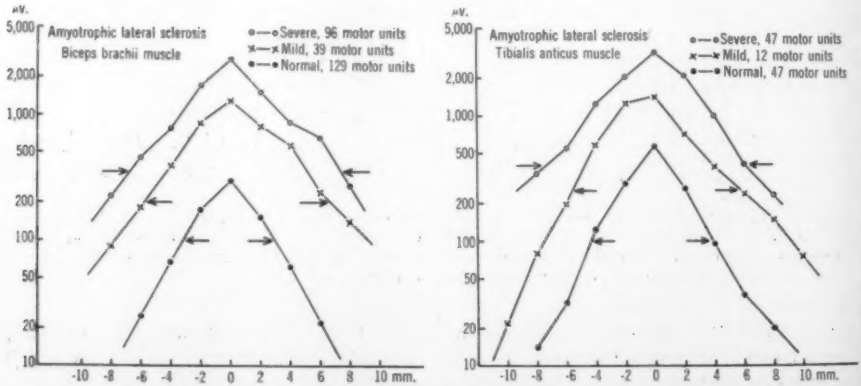

Fig. 7. Voltage variation over motor units of muscles paretic from amyotrophic lateral sclerosis (m. biceps brachii and m. tibialis anterior). O——O severely involved muscles, X——X slightly involved muscles, ●——● normal muscles. *Ordinate:* Voltage in μv. (logarithmic scale). *Abscissa:* Distance along the multilead electrode measured from the lead which recorded the potential of maximum voltage

TABLE 2

MOTOR UNIT TERRITORY AND MAXIMUM VOLTAGE IN PATIENTS WITH AMYOTROPHIC LATERAL SCLEROSIS

Muscle	Number of muscles	Number of motor units	Spike level in μv.	Territory in mm. — Mean value	Territory in mm. — Standard deviation	Maximum voltage in μv. — Mean value	Maximum voltage in μv. — Standard deviation
Severely involved muscles							
Biceps brachii	20	100	350	12.2 ± 0.4	4.2	3,000 ± 190	1,900
Tibialis anterior	14	49	400	12.5 ± 0.6	4.1	3,300 ± 300	2,000
Rectus femoris	7	22	400	14.3 ± 1.1	5.1	3,700 ± 500	2,300
Slightly involved muscles							
Biceps brachii	9	48	200	10.0 ± 0.7	4.9	1,600 ± 110	770
Tibialis anterior	5	14	250	9.8 ± 0.9	3.5	1,700 ± 300	1,000
Normal material							
Biceps brachii	24	129	100	5.1 ± 0.2	2.4	370 ± 20	190
Tibialis anterior	8	47	100	7.0 ± 0.4	3.0	620 ± 40	300
Rectus femoris	9	65	100	10.0 ± 0.6	4.6	550 ± 40	300

TABLE 3

MOTOR UNIT TERRITORY AND MAXIMUM VOLTAGE IN MUSCLES WITH AND WITHOUT SIGNS OF SPASTICITY. (m. biceps brachii and m. tibialis anterior)

State	Number of muscles	Number of motor units	Spike level in μv.	Territory in mm. — Mean value	Territory in mm. — Standard deviation	Maximum voltage in μv. — Mean value	Maximum voltage in μv. — Standard deviation
Muscles with spasticity							
Amyotrophic lateral sclerosis, severe paresis	13	49	310	11.8 ± 0.5	3.3	3,100 ± 230	1,600
Amyotrophic lateral sclerosis, spasticity without paresis	4	12	110	10.0 ± 1.1	3.9	500 ± 70	250
Cerebral thrombosis	3	14	100	8.5 ± 0.55	2.1	700 ± 110	400
Muscles without spasticity							
Amyotrophic lateral sclerosis, severe paresis	19	101	280	12.2 ± 0.4	3.9	3,300 ± 170	1,700
Normal subjects	16	103	100	6.1 ± 0.3	3.0	470 ± 25	240

TABLE 4

MOTOR UNIT TERRITORY AND MAXIMUM VOLTAGE IN PATIENTS WITH PERONEAL MUSCULAR ATROPHY AND SYRINGOMYELIA

Muscle	Number of muscles	Number of motor units	Spike level in μv.	Territory in mm. — Mean value	Territory in mm. — Standard deviation	Maximum voltage in μv. — Mean value	Maximum voltage in μv. — Standard deviation
Peroneal muscular atrophy							
Tibialis anterior	5	49	250	12.1 ± 0.4	3.1	4,200 ± 350	2,400
Syringomyelia							
Biceps brachii	4	32	150	6.9 ± 0.5	2.6	1,150 ± 120	660
Normal material							
Tibialis anterior	8	47	100	7.0 ± 0.4	3.0	620 ± 43	300
Biceps brachii	24	129	100	5.1 ± 0.2	2.4	370 ± 17	190

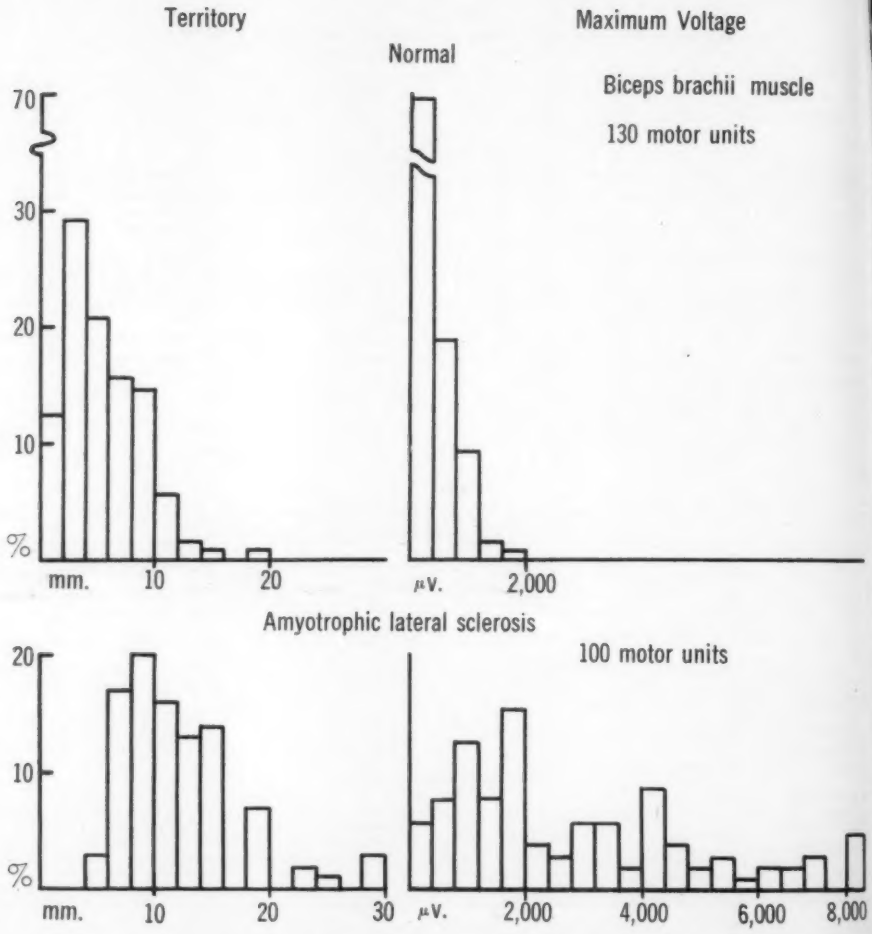

Fig. 8. Histograms of motor unit territory and maximum voltage in paresis due to severe amyotrophic lateral sclerosis *(below)*. For comparison, histograms are given for normal muscle *(above)*. *Abscissa:* Ranges of territory and maximum voltage. *Ordinate:* Percentage of motor units in each range.

DISCUSSION

In the study presented here, motor unit territory was mapped in paretic muscles by means of random insertions of a multilead electrode. This gives a true picture of the motor unit territory, since it has previously been shown that, in the muscles investigated, the area occupied by the fibers of a motor unit was circular and that eccentric insertions of the multilead electrode through this area did not influence to any appreciable degree the average values of territory.[7,8] Therefore, the variation in territory found in muscles with neurogenic paresis is due to actual differences in the extent of the different motor units as was the case in normal muscle (Figs. 5 and 8). The corre-

lation between motor unit territory and maximum voltage indicates that motor units with a large territory also have a high density of muscle fibers.

In the paretic muscles, maximum voltage and motor unit territory increased both when the paresis was due to anterior horn cell involvement and when it was caused by injury to the peripheral nerve, provided the injury had occurred eight months or more before the examination (Tables 1 and 2). The increase in territory indicates that included in the surviving motor units are muscle fibers that originally were situated outside the area of the motor unit. The increase in maximum voltage indicates that the motor unit contains a greater number of muscle fibers per unit area. This conclusion is based on the assumption that the electrical impedance around the active muscle fibers is of the same order as in normal muscle. A replacement of some muscle fibers by connective tissue does not change the impedance significantly, since inactive fibers act as insulators.[17] An increase in fiber concentration also is indicated in the finding of a higher voltage at which the spike components appear in the action potentials led off from the periphery of the motor units. With an increased fiber concentration, the potentials which are volume-conducted to the periphery of the motor unit have a higher voltage than in normal muscle. This increase in fiber concentration could be explained by the reinnervation of denervated muscle fibers through peripheral branching of nerve fibers originating from surviving motor units.[4–6] To a certain extent, peripheral branching can also account for the increase in territory.

The changes in motor unit territory and in maximum voltage after peripheral nerve injury are determined by 2 processes which partly compensate each other: [1] A reduction in diameter of denervated muscle fibers tends to decrease the cross-sectional area of the muscle and, therefore, to reduce the motor unit territory and to increase the fiber concentration of surviving motor units. The increase in fiber concentration is partly counteracted by the proliferation of connective tissue concomitant with the reduction in muscle fiber diameter. [2] Reinnervation due to peripheral branching to denervated fibers tends to increase both territory and fiber concentration of surviving motor units. In addition, new motor units are formed by the outgrowth of nerve fibers, the continuity of which was interrupted by the injury. No prediction is possible as to the size of these motor units.

That maximum voltage and motor unit territory remain largely unchanged within the first three months after the damage to a peripheral nerve (Table 1) is explained by the fact that the decrease in cross-sectional area of the muscle is substantially less than might be expected from the reduced muscle fiber diameter. This is due to proliferation of connective tissue. While the average muscle fiber diameter a few months after the onset of paresis is reduced to one-half or one-third the normal average,[18–20] the cross-sectional area of the muscle as calculated from the reduction of the muscle weight is reduced by only 30%.[19] This reduction in cross-sectional area would cause a decrease of 15% in average extent of the motor unit. A change of this order is too small to be detectable in the material presented here. The unaltered maximum voltage and spike level within three months after nerve injury indicate that reinnervation due to peripheral branching has not yet occurred to any appreciable degree.

That reinnervation has occurred in muscles examined eight months or more after nerve injury is indicated by increased maximum action potential voltage of the motor units, increased incidence of polyphasic potentials, and increased force as compared with the result of grading early after the injury.

Changes in maximum voltage and motor unit territory in paresis due to amyotrophic lateral sclerosis, spinal muscular atrophy (Werdnig-Hoffmann), and peroneal muscular atrophy (Charcot-Marie-Tooth) were much more pronounced than in paresis secondary to peripheral nerve injury, although the duration of the paresis was similar in the two groups (Tables 2 and 4). Even in slightly involved muscles, the maximum voltage within the motor units was 3 to 4 times greater than that of normal muscles, that is, similar to that of severely paretic muscles in which the paresis was due to peripheral nerve injury. In addition, in slight paresis secondary to anterior horn cell involvement, the motor unit territory was increased

to a larger degree than in severe paresis due to peripheral nerve injury.

The increase in average territory by 5 to 7 mm. in severely involved muscles in amyotrophic lateral sclerosis can hardly be accounted for by peripheral branching alone. Development of new nerve sprouts over a distance of 2.5 to 3.5 mm. would be required. From the histologic description, sprouting appears to be confined to much smaller distances.[6]

In normal muscle, there is evidence that the anatomically and electrophysiologically defined motor units are identical.[8] The findings in paresis secondary to anterior horn cell involvement might be interpreted in terms of a difference between these 2 units. For example, simultaneous activation of 2 anterior horn cells would be associated with 1 large electrophysiologic motor unit. One might object to this interpretation that the 2 synchronized units should each appear with its peak in the voltage variation across the cross section of the electrophysiologically defined motor unit. That voltage variations with 2 peaks are, in fact, rare might be due to the reinnervation of muscle fibers from denervated motor units situated between the syncronized motor units. Synchronized activity of different anterior horn cells might result from an increase in excitability, so that a discharge of 1 surviving anterior horn cell causes activation of neighboring cells.[9,10,12]

For the following reasons, the increase in maximum voltage and in motor unit territory in paretic muscle is not due to the selection of those motor units which in normal muscle are recruited only at strong effort.

1] Although, at random recording, later recruited motor unit potentials have a higher voltage than the firstly recruited potential,[21] *maximum* voltage and motor unit territory did not differ in successively recruited motor units.[8]

2] A selective loss of small motor units seems improbable in paresis secondary to peripheral nerve injury.

3] In paresis secondary to involvement of the anterior horn cells, a substantial percentage of motor units have maximum voltages and territories which exceed the values found in normal muscle (Fig. 8).

It is characteristic of muscles paretic due to anterior horn cell involvement that single motor unit potentials can be discriminated in the electromyographic pattern of maximum effort without interference from discharges originating from neighboring motor units.[9] This was the case even in muscles in which the force reduction was only slight (force graded as 4+ or more). In view of the large territory occupied by the fibers of the individual motor units, this implies that, in these muscles, the total number of electrophysiologically defined motor units is small. An exact evaluation of the number of muscle fibers per motor unit in these muscles is not feasible because the relationship between fiber concentration and maximum action potential voltage is unknown. The increased territory alone implies an increase in motor unit area in severely paretic muscles by a factor of 6 in the brachial biceps and by a factor of 3 in the anterior tibial muscle (Table 2). Assuming proportionality between fiber density and maximum voltage, the fiber concentration would be 8 times that of normal muscle in the brachial biceps and 5 times that of normal in the anterior tibial muscle. This would result in a 50 to 15 times larger number of muscle fibers per electrophysiologically defined motor unit as compared with normal muscles. Since the normal brachial biceps and the anterior tibial muscle contain 800 and 400 motor units, respectively,[22,23] and since force grading indicates that only half the normal number of muscle fibers contribute to the maximum effort, the number of motor units in these paretic muscles is estimated at 8 and 15 respectively.

That single motor unit potentials could be discriminated at maximum effort in muscles in which the paresis was only slight (force graded as 4+ or more) indicates that the enlargement of the electrophysiologically defined motor unit appears before a substantial loss of muscle fibers has manifested itself.

Whether spasticity was present in severely paretic muscles of patients with amyotrophic lateral sclerosis did not affect the average values of maximum voltage and motor unit territory (Table 3). Spastic muscle without paresis showed an increase in territory but no change in maximum voltage. This indicates that peripheral sprouting cannot have caused a significant increase in fiber density. The same applies to highly spastic muscles from pa-

TABLE 5

RANGES OF MAXIMUM VOLTAGE AND MOTOR UNIT TERRITORY IN THE BRACHIAL BICEPS TO DIFFERENTIATE BETWEEN PARESES OF DIFFERENT CAUSE

	Range of Maximum voltage (μv.)	Range of Territory (mm.)
Severe paresis due to		
Amyotrophic lateral sclerosis	>2,000	>9.5
Peripheral nerve injury*	600—2,000	6—9.5
Normal muscle	<600	<6.0

*Examined more than eight months after the injury

tients with hemiparesis due to cerebral thrombosis.

In syringomyelia, there was an increase in fiber density within the motor units but no increase in territory; that is, findings were similar to those in slightly involved muscles in amyotrophic lateral sclerosis. It is very likely that the more severely paretic distal muscles would have shown an increased territory as well.

Statistical evaluation of the findings for purposes of differential diagnosis. In the diagnostic application of the findings described, 2 questions pose themselves: With values of territory and maximum voltage for a small number of motor units as can be obtained in a single muscle, [1] do they deviate significantly from values of normal muscle, and, [2] if so, are the changes due to paresis caused by injury to the peripheral nerve or secondary to anterior horn cell involvement.

To answer these questions, the average values of maximum voltage and motor unit territories in the brachial biceps are considered, with the respective standard deviations listed in Tables 1 and 2. Based on these average values, suitable ranges of maximum voltage and territory were chosen to differentiate between the normal muscle, muscles severely paretic due to peripheral nerve injury, and muscles paretic due to severe anterior horn cell involvement (Table 5).

In Table 6, probabilities are given that territories and maximum voltages (obtained from 6, 9, and 12 different motor units) belong to the 3 ranges given in Table 5. These probabilities were obtained from the average values and standard deviations listed in Tables 1 and 2. In this calculation, a gaussian distribution was assumed for both territories and maximum voltages in different motor units. That this assumption is reasonable is seen from the histograms of Figures 5 and 8. The probabilities given in Table 6 show that the chosen intervals of maximum voltage and territory (Table 5) in fact allow a differentiation between a normal and a pathologic state of the muscle on the one hand and between paresis due to peripheral nerve injury and to anterior horn cell involvement on the other hand. This is illustrated by the following examples:

Differentiation between a normal and a paretic muscle. With values from 6 different motor units, an average maximum voltage exceeding 600 μv. occurs with an incidence of only 0.2% in normal muscle as compared with an incidence of 95 to 96% in paretic muscles. The probability of obtaining an average territory exceeding 6 mm. is 18% in normal and 88 to 100% in paretic muscles.

Differentiation between paresis due to peripheral nerve injury and secondary to anterior

TABLE 6

PROBABILITY IN PER CENT OF AVERAGE VALUES OF MAXIMUM VOLTAGE AND MOTOR UNIT TERRITORY TO BE LOCATED WITHIN ONE OF THE RANGES GIVEN IN TABLE 5

Severe paresis due to	Number of motor units examined	Average maximum voltage in μv. >2,000	600–2,000	<600	Average territory in mm. >9.5	6–9.5	<6
Amyotrophic lateral sclerosis	6	90.2%	6.3%	3.5%	94.3%	5.7%	0%
Peripheral nerve injury	6	4.9%	90.1%	4.9%	2.3%	85.8%	11.9%
Normal muscle	6	0%	0.2%	99.8%	0%	18.4%	81.6%
Amyotrophic lateral sclerosis	9	94.3%	4.4%	1.3%	97.3%	1.2%	0%
Peripheral nerve injury	9	2.2%	95.6%	2.2%	0.7%	94.5%	5.2%
Normal muscle	9	0%	0%	100.0%	0%	9.9%	90.1%
Amyotrophic lateral sclerosis	12	96.6%	2.9%	0.5%	98.8%	1.2%	0%
Peripheral nerve injury	12	1.0%	98.0%	1.0%	0.3%	94.5%	5.2%
Normal muscle	12	0%	0%	100.0%	0%	9.9%	90.1%

horn cell involvement. With values from 6 different motor units, an average maximum voltage between 600 and 2,000 μv. is 15 times more probable in severe paresis due to peripheral nerve injuries than in severe paresis due to amyotrophic lateral sclerosis. Conversely, an average maximum voltage exceeding 2,000 μv. is 18 times more probable in severe amyotrophic lateral sclerosis than in paresis due to peripheral nerve injury. An average territory of 6 to 9.5 mm. is 15 times more probable in paresis due to peripheral nerve injury than in severe amyotrophic lateral sclerosis; a territory exceeding 9.5 mm. is 40 times more probable in paresis due to amyotrophic lateral sclerosis than in paresis due to peripheral nerve injury.

SUMMARY

The changes in motor unit organization which accompany paresis caused by traumatic lesions of the peripheral nerve and paresis secondary to involvement of the anterior horn cells are described. By means of multilead recording, the spread of the action potentials of a motor unit over the cross section of the muscle and the maximum voltage within the motor unit were determined. The spread of the action potentials is a measure of the territory of the motor units and the maximum voltage, a gauge of the density of muscle fibers within it.

In *paresis secondary to peripheral nerve injury* investigated eight months or longer after nerve injury, the maximum voltage was 2.4 to 3.5 times that of normal muscle and the motor unit territory was increased by an average of 15 to 40%, depending on the muscle investigated.

In muscles in which the motor nerve supply was damaged less than three months before the investigation, the maximum voltage was 1.8 times that of normal muscle in the deltoid and unchanged in the brachial biceps and the extensor digitorum communis. The motor unit territory was within the limits of normal muscle.

The changes in motor unit territory and maximum voltage did not correlate with the degree of paresis as determined by muscle grading.

In *paresis due to involvement of the anterior horn cells* (amyotrophic lateral sclerosis and spinal muscular atrophy [Werdnig-Hoffmann] the increase in motor unit territory and maximum voltage exceeded by far that of equally paretic muscles in peripheral nerve injuries. In severely involved muscles, the maximum voltage was 5 to 8 times that of normal muscle and the motor unit territory was increased by 80 to 140%. A considerable fraction of motor units had territories and maximum voltages never found in normal muscle.

In less involved muscles, the values of territory and maximum voltage were in between those of severely involved and normal muscles, the maximum voltage being increased by 3 times and the territory by 40 to 130% as compared with normal muscle.

Findings in *peroneal muscular atrophy* (Charcot-Marie-Tooth) were similar to those in amyotrophic lateral sclerosis. In *syringomyelia*, the motor unit territory was unchanged as compared with normal muscle but maximum voltage was increased 3 times.

The increase in territory observed in neurogenic paresis of peripheral and central origin indicates that muscle fibers are included in the surviving motor units which originally were situated outside the area of these motor units. The increase in maximum voltage indicates that the motor units contain a greater number of muscle fibers per unit area. This increase in fiber concentration can be explained by the reinnervation of denervated muscle fibers through peripheral branching of nerve fibers from surviving motor units. The increase in motor unit territory of 5 to 7 mm. in paretic muscles in amyotrophic lateral sclerosis is thought to be due to synchronized activity of different anterior horn cells causing an enlargement of the electrophysiologically defined motor units. There is evidence that the enlargement of the electrophysiologically defined motor unit precedes loss of muscle fibers.

A statistical evaluation of the findings is given for purposes of differential diagnosis.

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Effect of convulsions on cerebrospinal fluid and plasma activity of glutamic oxalacetic transaminase and lactic dehydrogenase

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INCREASED CEREBROSPINAL FLUID glutamic oxalacetic transaminase (GOT) activity has been reported in dogs with experimental cerebral infarction,[1] and elevation of cerebrospinal fluid GOT and lactic dehydrogenase (LDH) activity has been observed in humans with cerebrovascular accidents and convulsions.[2-6] The blood-cerebrospinal fluid barrier[7-10] normally prevents transfer of GOT from plasma to cerebrospinal fluid. We have found, however, that prolonged seizures in puppies increase the permeability of the blood-cerebrospinal fluid barrier as determined by the marked increase in the transfer of radioiodinated human serum albumin (RIHSA) from plasma to the cerebrospinal fluid.[11]

The purposes of this study were to evaluate (1) the effect of prolonged convulsions on the cerebrospinal fluid and plasma GOT and LDH activity in puppies and (2) whether the increased enzyme activity in the cerebrospinal fluid reflects changes in blood–cerebrospinal fluid barrier permeability.

METHOD

Convulsions were induced in 40 puppies, aged 2 to 6 months, for periods varying from twenty-four to one hundred sixty-three minutes by either electroshock or Metrazol. Eighteen puppies receiving electroshock were placed in a hanging harness, especially devised for this purpose, which eliminated the need for any sedation during the period of convulsions. Moist electrodes were applied over the skin of the temperoparietal region. Electroshock was administered for periods of ten to fifteen seconds, starting with 100 to 120 volts and increasing by 10 volts at each shock. Rest periods of one to one and one-half minutes were allowed after the cessation of each seizure before a new shock was applied. A maximum of 480 volts was used. An average of 30 shocks was given to each experimental animal, since an attempt was made to continue seizures for at least sixty minutes. A maximum of seventy-nine minutes of active convulsions was obtained. The puppies studied in this group usually survived the effects of the electroshock convulsions.

Twenty-two puppies received 50 to 60 mg. of intravenous Metrazol per kilogram of body weight. Convulsions followed within ten to fifteen seconds. In a few animals, convulsions ceased after ten to fifteen minutes and an additional injection of 20 mg. per kilogram of body weight was given intraperitoneally so that the total convulsion time could be prolonged. The duration of the convulsions varied from twenty-four to one hundred sixty-three minutes. Many of the puppies expired from the effects of the continued seizures produced by this method.

In both groups of experimental animals, 1 gm. of glucose in 10 cc. of water was administered subcutaneously before the production of convulsions and additional injections of 0.5 gm. were given at intervals throughout the ex-

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periment. A total of approximately 3 gm. of glucose was given during each procedure. In the group treated with electroshock, the animals tolerated a larger number of shocks when glucose was administered; in the Metrazol group, the survival time appeared to be prolonged and more severe seizures were observed.

Pentobarbital sodium (in doses of 25 mg. per kilogram) was administered intraperitoneally as an anesthetic at the termination of the convulsive period so that cisternal fluid might be obtained.

Heparinized blood samples and 2 cc. of cisternal fluid were obtained at the termination of convulsions. Plasma was separated from erythrocytes after centrifugation at 3,000 rpm for five minutes. Specimens were stored frozen and enzyme determinations performed within a week. Cisternal fluid containing erythrocytes was centrifuged and separated immediately to avoid high values from hemolysis. Plasma specimens showing hemolysis were discarded.

In those animals in which convulsions terminated in death, blood had to be obtained by cardiac puncture and could not be used for enzyme determinations because of the possibility of tissue contamination, which would raise the enzyme activity.

Sixteen puppies used as controls were treated by a sham procedure, and cisternal fluid and plasma specimens were obtained at intervals corresponding to those in the experimental group.

GOT activity was determined in the 40 experimental puppies and 16 controls using the technic described by Karmen;[12] LDH activity was measured in 26 experimental puppies and 14 controls using the method of Wroblewski and La Due.[13] All determinations were performed at approximately 25° C.

RIHSA in doses of 11 μc. per kilogram of body weight was given intravenously to all experimental and control puppies to evaluate the permeability of the blood/cerebrospinal fluid barrier by measuring the rate of passage of isotope from blood to cerebrospinal fluid. The isotope was injected just prior to the institution of seizures in the experimental group. Cerebrospinal fluid and plasma in samples of 1 and 0.1 cc., respectively, were measured in

TABLE 1

CEREBROSPINAL FLUID AND PLASMA GOT AND LDH ACTIVITY IN NORMAL PUPPIES AND IN PUPPIES IMMEDIATELY FOLLOWING CONVULSIONS

Type of assay	Control			Convulsions			p	Average change %
	No. of cases	Range units/cc/min.	Average ± S.D.* units/cc/min.	No. of cases	Range units/cc/min.	Average ± S.D.* units/cc/min.		
Cerebrospinal fluid:								
GOT	16	1.0 — 3.25	2.04 ± 0.23	40	2.0 — 20.0	7.71 ± 3.87	< .01	+ 278
LDH	14	1.11— 6.67	4.46 ± 1.77	26	4.44— 38.4	13.65 ± 8.18	< .01	+ 206
Plasma:								
GOT	12	4.0 — 38	12.4 ± 8.02	16	14 — 108	39.6 ± 25.7	< .01	+ 219
LDH	10	90 —520	239 ± 135	11	250 —1,170	720 ± 339	< .01	+ 202

*Standard deviation

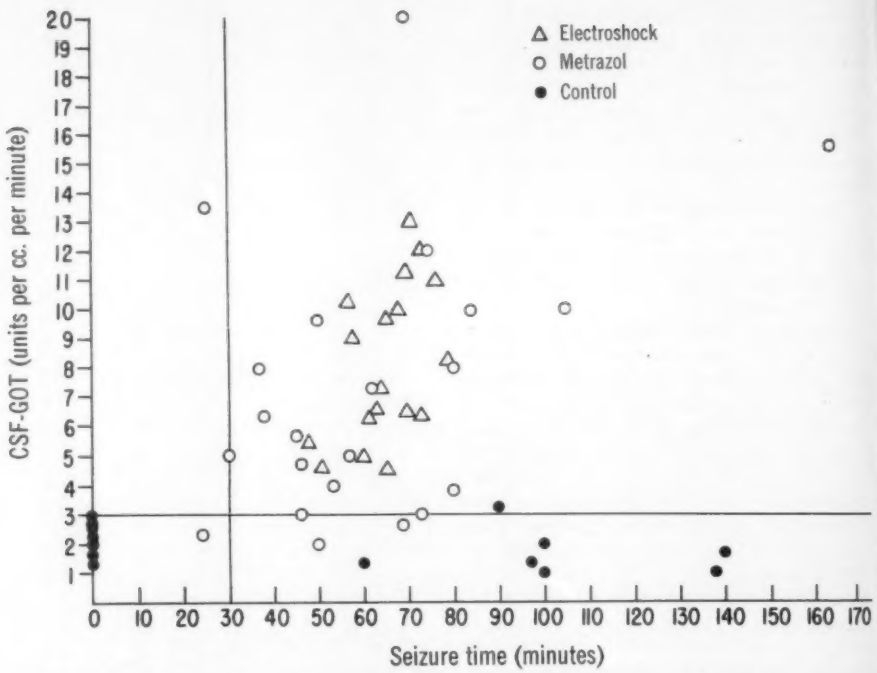

Fig. 1. Cerebrospinal fluid GOT activity as a function of time following prolonged convulsions in individual puppies. Control points at other than zero time indicate puppies treated with I^{131} and sham procedure for given periods prior to cisternal tap.

a well-type scintillation counter and recorded as counts per cubic centimeter per minute. Concentration ratios of cisternal fluid radioactivity to plasma radioactivity were calculated from these readings. After precipitation of the protein in a sampling of the specimens obtained, no significant radioactivity was found in the filtrate. Since metabolic degradation of the labeled albumin occurs at the rate of 9 to 13% per day,[14] the maximum amount degraded over the longest period in this experiment (three hours) would be less than 2%. Significant contamination of labeled albumin with nonprotein-bound I^{131} therefore would not be anticipated.

RESULTS

The average activity of GOT and LDH in both the cerebrospinal fluid and plasma of the experimental group with prolonged convulsions was approximately 3 times higher than that in the control group (Table 1). Convulsions induced by either Metrazol or electroshock produced essentially similar results.

When convulsions continued for periods of thirty minutes or longer, cerebrospinal fluid enzyme activity levels, plotted as a function of seizure time (Figs. 1 and 2), showed an increase in the majority of puppies: GOT 87.5%; LDH, 73.2%. The increased activity was considered significant if it was above the upper limit of normal as determined in the control series: GOT, 3.25 units per cubic centimeter per minute; LDH, 6.7 units per cubic centimeter per minute.

Five puppies were followed with repeat cisternal taps at varying intervals of two to four days over a period of one week following the seizures. The cerebrospinal fluid enzyme activity in this group was highest immediately after

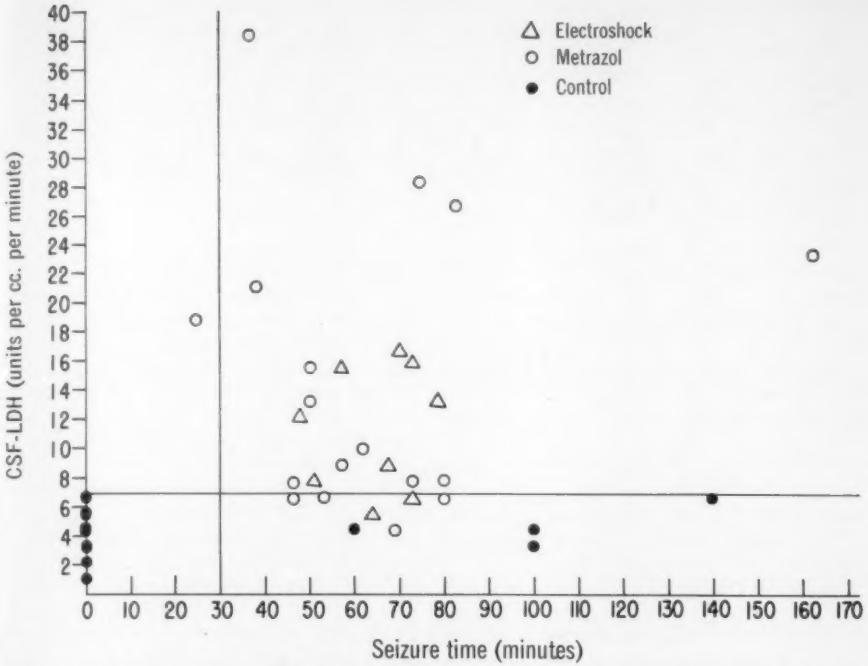

Fig. 2. Cerebrospinal fluid LDH activity as a function of time following prolonged convulsions in individual puppies. Control points at other than zero time indicate puppies treated with I^{131} and sham procedure for given periods prior to cisternal tap.

the convulsions and decreased over the subsequent days.

In a previous study[15] which demonstrated that changes in the permeability of the blood–cerebrospinal fluid barrier could be evaluated by the rate of passage of tagged albumin from the blood to the cisternal fluid, the concentration ratios of cisternal fluid radioactivity to plasma radioactivity in normal puppies did not exceed 60×10^{-5}. Higher ratios indicated an increase in permeability of the blood–cerebrospinal fluid barrier. In 27 of 29 puppies in which convulsions were prolonged beyond thirty minutes, the concentration ratios exceeded 60×10^{-5} (range: 67.1×10^{-5} to $2{,}378 \times 10^{-5}$).

Cerebrospinal fluid/plasma ratios of GOT and LDH were determined in all cases where blood could be obtained by venipuncture. Cardiac blood specimens were not included since comparison of venous and cardiac blood enzyme activities in several puppies showed both GOT and LDH activity to be higher in cardiac blood.

The cerebrospinal fluid/plasma radioactivity ratios with albumin-I^{131} were markedly increased in the experimental animals as compared to the control animals; the average was approximately 20 times as great. The cerebrospinal fluid/plasma enzyme activity ratios were essentially the same in both the control and experimental animals. These were much greater than the cerebrospinal fluid/plasma radioactivity ratios obtained using albumin-I^{131} (Table 2).

DISCUSSION

In our series of normal puppies, the cerebrospinal fluid GOT (average: 2.04 units per cubic centimeter per minute $\pm$ 0.23 units) and plas-

TABLE 2
CEREBROSPINAL FLUID TO PLASMA RADIOACTIVITY AND ENZYME RATIOS

CSF/Plasma ratio	Control			Convulsions			Mean increase %
	No. of cases	Average	Range	No. of cases	Average	Range	
$I^{131} \times 10^{-5}$ *	7	29.0	14.8— 61.0	11	592.5	67.1—2,378.3	1,943.0
GOT $\times 10^{-2}$	13	187.8	52.6—417.5	16	251.1	89.8— 480.0	33.7
LDH $\times 10^{-2}$	11	23.7	0.7— 49.4	11	19.1	5.4— 35.9	—

*Cases with GOT and LDH ratios only

ma GOT (average: 12.4 units per cubic centimeter per minute $\pm$ 8.02 units) activity is lower than that previously reported in older dogs by Wakim and Fleisher.[1] Their normal dogs (using a conversion factor of 1 unit per cubic centimeter per minute = 0.044 micromol per cubic centimeter per hour) showed average serum values of 23.8 units per cubic centimeter per minute and cerebrospinal fluid of 15 units per cubic centimeter per minute. This is probably due to the difference in age of the animals, since none of the puppies in the present series was over 6 months old.

Miyazaki[6] recently showed elevation in the cerebrospinal fluid GOT in patients with convulsive disorders if determinations were performed during or immediately after the seizures. He speculated that this increase was due to alterations in cell membrane permeability.

In the present study, there was a markedly increased permeability of the blood-cerebrospinal fluid barrier to albumin as determined by the elevated ratios in the convulsed group of puppies. Elevated cerebrospinal fluid enzyme levels were observed, but ratios were not elevated over those found in the controls. In the face of similar molecular weights of the 2 proteins (GOT, 60,000; albumin, 69,000), there could be 3 possible explanations: (1) a selective passage from blood to cerebrospinal fluid independent of molecule size, (2) increased transfer of cerebrospinal fluid GOT and LDH from the cells of the central nervous system rather than from the blood, or (3) a combination of the 2 preceding factors. The similarity in GOT and LDH ratios in the control and experimental puppies would be expected if there were no change in permeability of the blood-cerebrospinal fluid barrier. Since in the convulsed puppies the mean increase in plasma activity was essentially similar to that in the cerebrospinal fluid, it is probable that the increased muscular activity during the prolonged seizures plays a major role in discharging enzymes into the circulation and so elevating the blood enzyme activity. This suggests that increased transfer from the brain cells must be a major source of the cerebrospinal fluid enzyme activity.

Wakim and Fleisher,[1] in serial studies, found higher levels of cerebrospinal fluid GOT about one hundred hours after the production of experimental cerebral infarction in dogs. The enzyme activity decreased over the subsequent period but did not come down to preinfarction levels even after fifteen days. In this study of puppies with convulsions, follow-up of plasma and cerebrospinal fluid enzyme activity in 5 puppies over a period of one week showed the maximum increase at the termination of seizures and a decrease thereafter, reaching normal values within a week. Since dogs with known cerebral tissue necrosis do not show maximum elevated enzyme activity until about one hundred hours after injury and since those with convulsions show highest activity immediately after the seizures, gradually decreasing thereafter, it is difficult to accept cellular lysis as contributing significantly to the immediate increase in enzyme activity. Wroblewski and associates[16] have shown by in vitro and in vivo studies of LDH activity that alterations in body fluid enzymes may occur in the absence of tissue necrosis.

Considering the aforementioned facts, increased cerebral cell membrane permeability rather than actual cerebral cell lysis is probably the major factor in the increase observed in the cerebrospinal fluid enzyme activity immediately following prolonged seizures. Increased permeability of the blood–cerebro-

spinal fluid barrier is apparently not of prime importance.

SUMMARY

The effect of prolonged convulsions induced by Metrazol or electroshock on plasma and cerebrospinal fluid GOT and LDH activity was studied in 40 puppies. Seizures of longer than thirty minutes' duration produced plasma and cerebrospinal fluid activity of GOT and LDH that was approximately 3 times greater than in controls. The mean increase in plasma enzyme activity was similar to that in the cerebrospinal fluid.

Cisternal fluid/plasma radioactivity concentration ratios of albumin-I^{131} were measured concomitantly with the enzyme determinations and demonstrated increased permeability of the blood–cerebrospinal fluid barrier to albumin. Cisternal fluid/plasma GOT and LDH ratios were essentially similar in the control and experimental groups, suggesting no major increase in permeability of the blood–cerebrospinal fluid barrier to these enzymes.

Elevated cerebrospinal fluid GOT and LDH activity immediately following prolonged seizures probably reflects an increase in cerebral cell membrane permeability rather than actual cellular lysis, and increased permeability of the blood-cerebrospinal fluid barrier to the enzymes is apparently not a major factor.

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The electroencephalogram in internal carotid artery occlusion

Fletcher McDowell, M.D., Charles E. Wells, M.D., and Carol Ehlers

DURING THE PAST SEVERAL YEARS, the importance of occlusion of the internal carotid artery as a cause of cerebral infarction has become increasingly apparent. In a recent study, McDowell and associates[1] found occlusion of the internal carotid artery in 16% of patients with cerebrovascular accidents who were investigated by carotid arteriography. While adjuvant methods, such as ophthalmodynamometry, auscultation of the cranium for bruits, observations of the conjunctival vessels, and pharyngeal palpation for the internal carotid pulse, have been advocated to aid the clinician in the diagnosis of this condition, little attention has been given to the electroencephalogram. Arteriography has usually been regarded as the diagnostic method of choice.

In their report of 30 patients with thrombosis of the internal carotid artery in the neck, Gurdjian and Webster[2] noted that delta activity usually appeared in the parietotemporal region on the affected side early in the course of the disease, with improvement in the electroencephalographic patterns with passage of time. Negrin[3] observed a flattening of the record over the involved hemisphere in 5 patients.

METHODS

For the past thirty months, electroencephalograms have been performed on all patients with suspected internal carotid artery occlusion who were admitted to the Second (Cornell) Neurological Service of Bellevue Hospital or to the neurology service of The New York Hospital. During this time, electroencephalograms have been performed on 20 patients having thrombosis of the internal carotid artery. Diagnosis was proved in each instance by carotid arteriography which demonstrated occlusion. In 18 patients, unilateral occlusion was demonstrated; in 1, bilateral occlusion; and in 1, incomplete occlusion. There were 15 male and 5 female patients. The ages of the patients varied from 37 to 72 years, with 15 being in the sixth and seventh decades. The site of occlusion was on the right side in 11 patients and on the left in 8.

A total of 36 electroencephalograms was made on the 20 patients, at periods varying from four days to six years after the onset of clinical symptoms. In 12 patients, the initial electroencephalogram was made within two weeks after the beginning of symptoms.

RESULTS

In all 20 patients, the electroencephalograms were considered to be abnormal. The most prominent electroencephalographic abnormalities were the presence of diffuse low amplitude slow wave activity and the presence of superimposed focal higher amplitude slow wave activity. In 19 of the patients, diffuse slowing of the brain wave activity was noted, predominantly in the theta range. This was usually confined to the side of the lesion, but at times the slowing involved both hemispheres. In addition and perhaps most striking, 19 patients exhibited prominent focal slow wave abnormalities, usually consisting of mixed theta and delta activity of high amplitude, standing out quite clearly from the diffuse low amplitude slowing of the background activity (Figs. 1, 2, and 3). This focal slow wave activity was present on the side of the circulatory insuffi-

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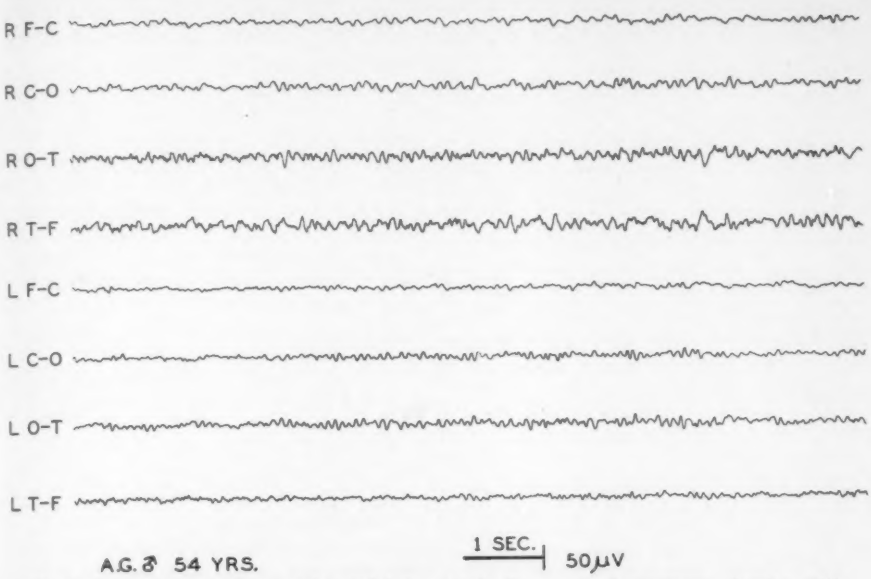

Fig. 1. Electroencenphalogram taken indefinite period after onset of symptoms, showing mild diffuse right sided abnormality with focal abnormality in right frontotemporal region

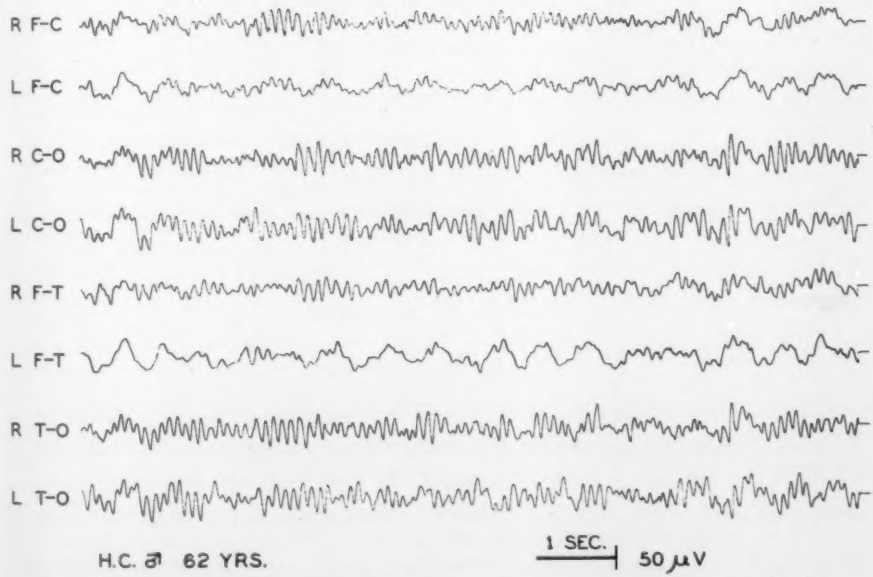

Fig. 2. Electroencephalogram taken twelve days after clinical onset, showing prominent high amplitude delta focus in left frontotemporal region

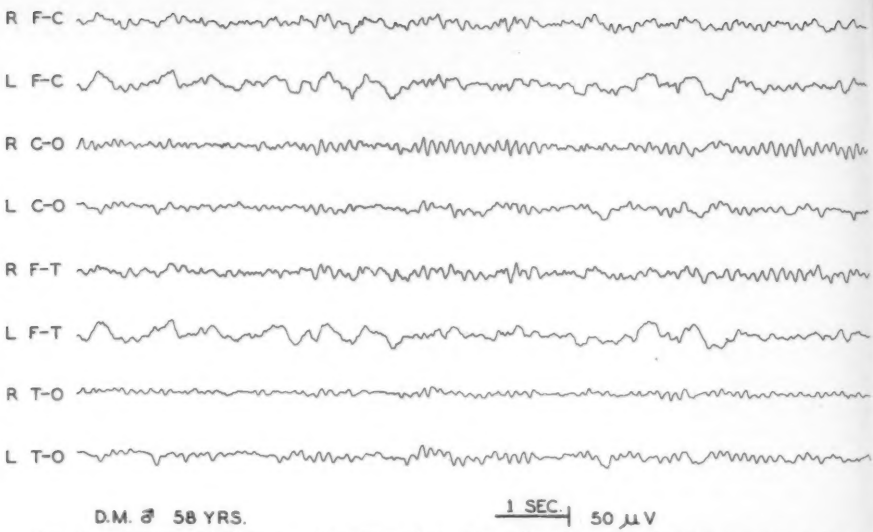

Fig. 3. Electroencephalogram taken seven days after clinical onset, showing prominent left frontotemporal delta focal abnormality and a more diffuse background abnormally involving the entire left hemisphere and the right frontal region as well

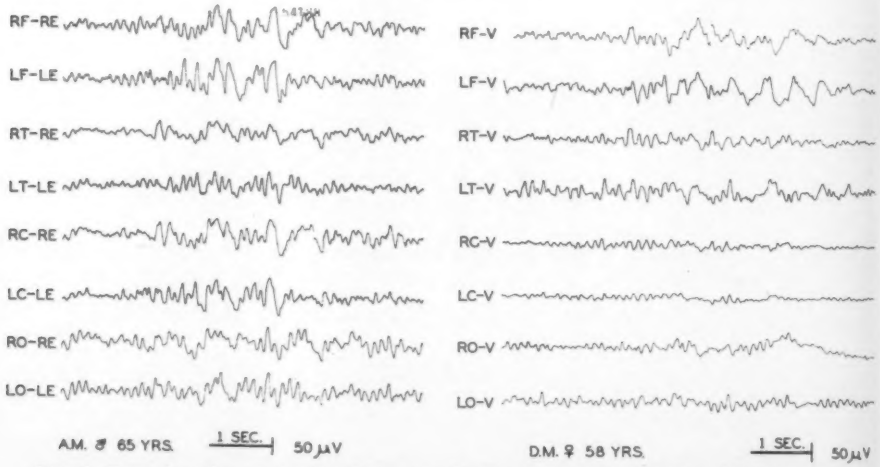

Fig. 4. Examples of paroxysmal activity occurring fourteen and twelve days following onset, respectively

ciency in 16 patients, but, in 3, it was found on the side opposite to the arteriographically demonstrated internal carotid occlusion. The focal slow wave activity was localized in the frontotemporal region in 10 patients, in the temporal region in 4, in the frontal region in 2, and in the temporooccipital region in 2. In 1 patient, no focal abnormality was demonstrated. The severity of the electroencephalographic changes appeared to bear little re-

lation to the severity of the clinical symptoms.

In addition, paroxysmal discharges occurred in 7 patients (Fig. 4). These discharges usually consisted of outbursts of high amplitude delta or theta activity lasting several seconds, followed by return to the more prevalent background activity. In 2 patients, these paroxysmal discharges were focal, but, in 5, they were bilateral and diffuse.

In patients followed serially, there was usually slow improvement, though the electroencephalogram often remained markedly abnormal for many weeks or months. Indeed, 1 patient who was examined six years following the onset of his clinical symptoms still demonstrated focal abnormalities.

DISCUSSION

These electroencephalographic abnormalities, while quite consistent within the group studied, are probably not specific for internal carotid occlusion, since they might also be expected to appear in other varieties of occlusive vascular disease. They frequently resemble the patterns seen in cerebral neoplasm, though the abnormalities in the background activity are more marked than those usually seen in cerebral tumor. The focus of high amplitude slow activity, however, may be indistinguishable from that often seen with a tumor. The most important differential point is that the record tends to improve with time in internal carotid occlusion, while this is not usually the case in cerebral neoplasm

The occurrence of the major abnormality on the side opposite the thrombosis in several instances is difficult to explain, but it is a finding which has been previously noted following surgical occlusion of the internal carotid artery.[4]

SUMMARY AND CONCLUSION

Electroencephalograms were performed on 20 patients having thrombosis of the internal carotid artery, all proved by arteriography. Electroencephalographic findings of significance were:

1. Diffuse low amplitude slow wave activity in 19 patients, usually confined to the side of the lesion but at times appearing bilaterally
2. Focal higher amplitude slow wave activity, usually mixed theta and delta, in 19, on the side of the insufficiency in 16
3. Slow improvement usually in patients followed serially, though the electroencephalogram might remain abnormal for many weeks.

While these changes are not specific, when the electroencephalographic findings are combined with clinical evaluation, ophthalmodynamometry, auscultation for bruits, and palpation of the internal carotid arteries in the pharynx, the diagnosis of occlusion of the internal carotid artery can often be made without resort to arteriography.

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Undergraduate attitudes toward the specialty of neurology

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FOR MANY YEARS, medical student folklore has leaned heavily on the belief that the difficulties of neurology are overwhelming. Sahs said in 1953, "There is no doubt that many students approach the subject of neurology with fear and apprehension." Wartenberg states, "Neurological examination is particularly dreaded by the practitioner because of its alleged complexities and intricacies. Neurology has the reputation among students as the most abstruse, remote and difficult discipline, full of high-sounding terms, with an elaborate technique of examination. The physician is ready to tackle any problem in medicine, however difficult, but shies away from a neurological problem. One of our jobs as instructors of neurology should be to try to simplify rather than to complicate this highly important subject."[1] Pearce Bailey said, "Another factor still operating against the promulgation of a national graduate program is the aura of therapeutic nihilism surrounding neurology. . . . One often hears the slogan that 'you can't make a living from the practice of neurology.'"[2]

Even though neurology has recently been reoriented toward a more dynamic and therapeutic approach, many young physicians still are reluctant to choose their careers in this field and many internists still have dangerously little knowledge of important principles of neurologic diagnosis and treatment.

In order to determine precisely what medical students at the University of Kansas School of Medicine find attractive or unattractive about neurology, a detailed questionnaire was evolved and circulated among upperclassmen and recent graduates. In this way, it was hoped to test the validity of the foregoing assumptions and get information which might prove helpful in interesting internists and other physicians in neurology, as well as in inducing more young doctors to enter the specialty.

MATERIAL AND METHODS

The four-year School of Medicine of the University of Kansas is part of the state-supported system of higher education. The medical school is an integral part of the University of Kansas Medical Center, a 600-bed general hospital, and the University of Kansas.

At the Medical Center, eleven clinical beds are assigned for the exclusive use of the Section of Neurology, which is in the Department of Medicine, and the section is the recipient of a training grant from the National Institute of Neurological Diseases and Blindness. Neurology also utilizes the 37-bed Neurology Service of the Kansas City, Mo., Veterans Administration Hospital for teaching at all levels. Until 1956, the section consisted of a single geographic full-time professor. Minor contributions to teaching were made by 2 part-time instructors. In 1956, the section acquired another full-time instructor, as well as a part-time instructor who shares equally in the teaching duties with the 2 full-time men.

The neurology curriculum at the University of Kansas consisted, at the time the questionnaire was sent out, of the following clinical courses: The third year students received a one-hour lecture-demonstration weekly for a period of six weeks. Fourth year students attended 15 two-hour formal lectures in neurology and attended 12 neurology outpatient clinics. Electives were available as summer clerkships in neurology. In October 1957, third and fourth year medical students and June 1957 graduates of the school were asked

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to cooperate in filling out a "Questionnaire on Medical Students' Attitudes Toward Neurology as a Specialty." There were approximately 100 students in each class.

RESULTS

Completed questionnaires were received from 39 third year students, 47 fourth year students, and 65 graduates, for a total of 151 answers. The following 4 groupings were made of the answers to the questionnaire:

A. Technical information about the professional aspects of neurology

B. The scope and content of neurology

C. The basic sciences of neurology

D. Attractive and unattractive features of neurology and factors affecting the choice of a specialty.

Respondents were 144 men and 7 women; 73% of them were married and 39% of them had at least 1 child. Of these, 86% made their homes in Kansas (for the purpose of this study, Kansas City, Mo.., was considered part of Kansas) and 38% came from towns with fewer than 15,000 inhabitants. The University of Kansas or some other college in Kansas had graduated 74%; 30% had a close relative who was a physician.

For the future, 28% planned to enter general practice, 24% were undecided, and 38% (57 respondents) wanted to enter a specialty. The last included 18 who chose internal medicine; 8, psychiatry; 7, general surgery; 4, pediatrics; 4, pathology; 2, obstetrics and gynecology; 2, neurology; and 1 each, physiatry, dermatology, radiology, plastic surgery, and aviation medicine. Undecided as to which specialty to enter was the response of 7.

QUESTIONNAIRE AND REPLIES

A. Technical information about the professional aspects of neurology

1. Length of formal residency training is:

2 years	6%	3 years	40%	4 years	20%
5 years	8%	6 years	2%	did not know	24%

(The following were in the form of statements to be answered by "Agree," "Disagree," or "Don't know.")

2. Financial compensation in neurology is usually less than that in most other branches of medicine.

Agree	16%	Disagree	39%	Don't know	45%

3. The length of postgraduate training in neurology is longer than in most other specialties.

Agree	21%	Disagree	57%	Don't know	22%

4. It is difficult to establish and maintain a purely neurologic practice because of the limited number of patients affected with diseases of the nervous system.

Agree	19%	Disagree	65%	Don't know	16%

5. Opportunities for teaching and research in neurology are limited at this time.

Agree	2%	Disagree	75%	Don't know	23%

6. Only the unusually gifted and intelligent physician should consider choosing neurology as a field of specialization.

Agree	14%	Disagree	78%	Don't know	8%

B. The scope and content of neurology

1. A neurologist is essentially an internist with a special interest in neurology.

Agree	80%	Disagree	18%	Don't know	2%

2. Most physicians, regardless of the type of practice or specialty, should have an adequate grounding in neurology.

Agree	99%	Disagree	0.5%	Don't know	0.5%

3. Neurology is strictly a diagnostic specialty offering little in the way of cure or treatment.

Agree	20%	Disagree	78%	Don't know	2%

4. Neurology and psychiatry are closely related and should be practiced together.
   Agree 30% Disagree 66% Don't know 4%
5. Neurosurgeons are generally capable of diagnosing and treating a neurologic illness or condition, and, thus, the neurologist is often superfluous.
   Agree 24% Disagree 62% Don't know 14%
6. Child neurology should be practiced by pediatricians, not by neurologists.
   Agree 6% Disagree 83% Don't know 11%
7. Neurology is unusually difficult to learn because of the large number of "name" syndromes (von Recklinghausen's disease, Foville's syndrome, Charcot's triad, and so on).
   Agree 46% Disagree 50% Don't know 4%
8. Neurology is still in its descriptive phase, and no major therapeutic advances have been made in it during the last twenty-five years.
   Agree 6% Disagree 82% Don't know 12%
9. The great majority of neurologic illnesses and conditions still remain mysterious in regard to etiology and pathogenic mechanisms.
   Agree 62% Disagree 30% Don't know 8%

C. The basic sciences of neurology

(Students were asked to indicate 1 or more answers to the following questions.)

1. Did you find neuroanatomy:

Difficult	39%	Average	26%	Easy	4%
Dull	8%	Interesting	70%		

2. Did you find neurophysiology:

Difficult	24%	Average	38%	Easy	2%
Dull	6%	Interesting	52%		

D. Attractive and unattractive features of neurology and factors affecting the choice of a specialty

(For the next questions, the students were asked to reply with a short paragraph.)

1. What appeals to you in neurology?

The close clinicoanatomical-mechanistic correlation in many neurologic conditions was mentioned by 46%. The challenge of difficult and interesting diagnostic problems appealed to 21%, while 10% felt that neurology offered unusually good opportunities for research and teaching.

2. What seem to you the most unattractive features in neurology?

The large number of incurable diseases and the poor prognosis and lack of treatment in neurologic conditions were mentioned by 53%. The many geriatric and institutional patients encountered in neurologic practice; children with "cerebral palsy;" patients with chronic illness and disability; and the psychiatric manifestations of neurologic disorders were mentioned by 13%. Another 13% mentioned the complexity of the field, the emphasis of terminology, and the endless classification, while 8% felt that neurology was too limited in scope.

3. Did anything or anyone in your medical school career contribute to making neurology more attractive to you as a possible field of specialization?

The personality and teaching ability of the instructors in neuroanatomy and clinical neurology were mentioned by 45% of the students. In addition, the courses in neuroanatomy, neurosurgery, and clinical neurology were mentioned by 11%, 22%, and 35%, respectively.

4. Did anything or anyone in your medical school career contribute to making neurology less attractive to you as a possible field of specialization?

The instructors were mentioned by 6% and the way the courses were presented by 4% of the respondents.

5. What would attract you to any particular field of specialization?

The desire to enter a specialty that would be interesting and provide intellectual stimulation was mentioned by 48%. The need for personal satisfaction in performing the job they had trained for was spoken of by 27%. Opportunities for research, teaching, and training and the need for specialists in the particular field were mentioned by 14%, while 10% felt that the type of patients encountered in such practice would be an important determinant. Working and living conditions (hours, size of town, and so on) concerned 9%, and 8% were concerned with the financial rewards attached to certain specialties. The personality and ability of the teachers of the particular specialty were mentioned by 8% of the respondents.

(Space was provided for comments at the end of the questionnaire. The following points were made.)

The long hiatus between the basic neurologic sciences (taught in the first year of medical school) and clinical neurology (taught in third and fourth years) made carry-over of information difficult; there was need for more clinical correlation during the teaching of the basic sciences; it was important to make neurologic teaching more interesting and practical; there was need for more clinical neurology in the curriculum. It was also suggested that the students be given more information about opportunities for practice, teaching, and research in neurology.

SIGNIFICANCE OF THE QUESTIONNAIRE

As in all studies involving the voluntary answering of questionnaires, the problem arises of whether the respondents constitute a representative and unbiased sample. In this investigation, approximately 39% of the third year students, 47% of the fourth year students, and 65% of the most recent graduates answered. Though a return rate of approximately 50% is a respectable figure, it is difficult to know whether these samples are representative of their entire classes. The possibility exists that those who answered the questionnaire were more conscientious, more "educationally" oriented, and more interested in neurology than were those who did not reply. It is understood, of course, that the observations in this study reflect only the attitudes of students and graduates of this medical school.

Our medical student population is a geographically homogenous one, as in most state schools of medicine. The state of Kansas is about half rural, and many ot its physicians are general practitioners. Even though 40% of the students know the exact duration of required residency training in neurology and 57% are aware that it is no longer than that required by most other specialties, there is still a sizable number of respondents who do not possess the correct information. Nonetheless, our students evinced a surprising sophistication in their answers to questions A4, A5, and A6 about the opportunities and difficulties of neurologic practice. These contradict the idea, long held by neurologists, that students are fearful of this branch of medicine.

From the answers to the next few questions, it is easy to see that the students are strongly interested in internal medicine. This may derive from a number of factors: that neurology is a section in the Department of Internal Medicine rather than an independent department; that the general medical services usually have a substantial number of neurologic patients on their wards; and the belief that the internist is the "basic" or "compleat" physician.

Our students have been impressed by the importance of neurology as a branch of medicine, and they should be receptive to more vigorous and extensive undergraduate teaching in neurology as part of their general medical education. It is evident that better neurologic training of all physicians, regardless of specialty, will result in better care of the neurologic patient.

The answers to B3 regarding the possibility of cure of neurologic ailments indicate that students are aware of new therapeutic possibilities in neurology despite the limited number of hours devoted to the subject in the curriculum.

From their answers, University of Kansas students seem to feel that neurology should be a distinct specialty or a subspecialty of inter-

nal medicine, separate from psychiatry, neurosurgery, and pediatrics. This is especially noteworthy in this school, since a total of two hundred ninety hours is devoted to psychiatry in the four years of medical school (a great deal more time than is assigned to neurology); the neurosurgeons have a large share in the teaching of neurology during the students' exposure to neurosurgery; the neurosurgeons in this area see a large percentage of nonsurgical neurologic patients because of the serious shortage of trained neurologists; and the Department of Pediatrics feels strongly that any diseases affecting children fall within the province of the pediatrician.

The students are almost equally divided (question B7) in finding the eponyms in neurology irritating or unobjectionable. It is noteworthy that, after exposure to clinical neurology, their distaste for the "name-syndromes" increases. The percentage of those who found them objectionable went from 38% among the third year students to 54% among the graduates. Although there has recently been a trend toward the use of eponyms in internal medicine (Hamman-Rich, Sjögren, Mikulicz, Stevens-Johnson, Reiter, Wegner, and so on), neurologic diseases remain, in most students' minds, synonymous with eponymic designations.

Students and teachers alike often say that the complexity of neuroanatomy and neurophysiology is a deterrent to students. This would seem to be untrue in our group, since the majority found both, especially neuroanatomy, interesting although difficult (C1 and C2). The instructor in neuroanatomy is functionally and clinically oriented and is generally regarded by the students as an inspiring teacher.

The most appealing feature of clinical neurology for 46% of the students was the possibility of making precise localizing diagnoses by utilizing their knowledge of neuroanatomy. In this light, it is evident that the quality of basic neurologic science instruction in a medical school is of extreme importance. The challenging diagnostic problems handled by the neurologist attracted 21% of the respondents. The many unknowns in neurology—still a virgin field for modern methods of investigation and perhaps one of the last frontiers in medicine—interested 10% of our students.

It was no surprise to learn that, to the students, the most unappealing part of neurology was the belief that the specialty deals mainly with a great many incurable diseases, illnesses that are difficult to control by medical or surgical methods, and ailments which result in early death or disability. This is a widespread and tenaciously held misconception. In many areas, neurologic diseases, such as the meningitides, epilepsy, cerebrovascular diseases, myasthenia gravis, and other diseases which can be treated and controlled, are handled by internists, pediatricians, and general practitioners because of the lack of trained neurologists.

The large number of geriatric and chronic patients encountered in neurology was mentioned as a deterrent by 13% of the respondents. This, however, is a reflection of the times. It indicates that our students are not sufficiently aware of the fact that in the future all physicians, save pediatricians and obstetricians, will find an increasing proportion of their practice devoted to gerontology and the management of chronic illness.

The personality and ability of their instructors was of great consequence in making neurology attractive, said 45% of the respondents. This factor even transcended the importance of the course material itself, although that also carried weight. This concept should be given consideration in selecting and training young doctors who plan to enter academic neurology.

The students' answers to the question on general factors affecting the choice of a specialty are not unexpected. The 27% of respondents who felt that a sense of accomplishment in their work ranks high in the choice were reiterating the truism that a physician's main purpose is to heal the sick. This is, of course, intimately involved with the myth that neurologists specialize in the incurable. Great significance was assigned by 10% to the type of patients encountered. Here again, chronic diseases, illnesses with psychiatric manifestations, and mentally retarded or crippled children are repugnant to many physicians.

DISCUSSION

Some valuable lessons may be derived from the answers to this questionnaire, and un-

doubtedly many more could be learned from similar questionnaires sent to medical students in schools with a different geographic distribution and educational climate. In general, our students appear to be well informed about the purpose and scope of neurology, despite the relatively few hours devoted to its study at the University of Kansas School of Medicine. We feel that the main purpose of neurologic education is not to recruit residents for neurologic training but to make every physician aware of the neurologic complications of his own specialty and the important role that neurology plays in all phases of medicine. A vigorous and enlightened teaching program at the undergraduate level will result indirectly in an increase in the number of physicians who choose to specialize in neurology.

Merritt has wisely pointed out that "the diagnostic phase of neurology is only a preliminary and not the end. The real goal is the care and the cure of the patient."[3] This has been the keynote of the neurologic revolution which has taken place since World War II. As far back as 1913, Dana sounded a warning of the impending danger that neurology might be compressed into a groove: "The neurologist must expand his interest or sink into the narrow niche of curator of the scleroses or an appraiser of teratological defects."[4]

In teaching students, instructors would do well to stress that neurology is no longer a narrow, descriptive, almost esoteric branch of medicine. There is not a single medical specialty, from obstetrics to dermatology, from orthopedic surgery to urology, in which the services of the well trained neurologist are not of vital necessity at some time. As Gregg said, "I have seldom seen expressed what seems to me the most important aspect of neurology; namely, that we cannot understand the whole organism until we understand nature's many mechanisms for keeping the separate organs integrated harmoniously into an organism. That is an important function of the nervous system. And it strongly corroborates the importance of neurology."[5] The growth of neurochemistry and neuropharmacology, the dynamic new orientation of neuropathology, and the realization that systemic metabolic defects affect the central nervous system have brought the brain and spinal cord out of their magnificent isolation within their bony envelopes.

Many students still believe that neurology and psychiatry are closely associated specialties. This idea is fostered by the fact that the certifying board remains the American Board of Psychiatry and Neurology. Even though their connection had sound historic background, developments in both specialties have made continued association almost anomalous. Knowledge of the various psychiatric syndromes is essential to the practice of neurology, but is this not also true in the practice of internal medicine? As a matter of fact, as the population ages, an increasing percentage of the diseases now handled by psychiatrists will be treated by neurologists. Cerebrovascular disease may well eventually displace schizophrenia as the major cause of "mental" disease in the same way that the latter replaced neurosyphilis. The formal association of neurology with psychiatry in the boards and in many medical schools seems spurious, since the technics and philosophies of the two are now so different. Forster has pointed out that "the old concept of a neuropsychiatrist is no longer tenable,"[6] and Percival Bailey's erudite appraisal of modern psychiatric methods has made this abundantly clear.[7]

The American Academy of Neurology has recognized the importance of pediatric neurology and created a special section dedicated to it. A few training programs specifically devoted to this subspecialty are already in existence today. The need to train teachers of neurology by giving them insight into educational methods and psychology and by acquainting them with administrative technics also has been given attention at the Institute of Neurological Sciences of the University of Pennsylvania and other training centers.

Along with the new emphasis on therapy has come a recognition of the unnecessary complexities of neurologic nomenclature and classification. Arrangement in groups serves a purpose only if it has practical or theoretic importance. As Merritt pointed out in his discussion of the classification of the muscular dystrophies, "There is no justification for these various subdivisions since they are all merely variations in the clinical picture of a single disease, and many of the supposedly charac-

teristic features of one form are present in patients who are classified under another form."[8] Greenfield[9] also attempted to clear a path in the eponymic jungle obscuring the spinocerebellar ataxias. If neurology seems complicated to the uninitiated, it is because neurologists themselves have made it so. In more and more instances, closer examination of different syndromes and application of modern concepts of disease have resulted in simplification of terminology.

An interesting insight into medical student psychology can be gained from the following quotation from Becker's "The Formation of Career Plans,"[10] a sociologic study carried out over a period of two years at the University of Kansas Medical Center:

> The views that students hold of particular specialties and the judgments they make as to their desirability revolve largely around two notions: first, to what degree does any specialty involve the doctor in the drama of medical responsibility; and second, to what degree does the specialty make use of the knowledge that the student has so painfully acquired in medical school. A "good" specialty is one in which the responsibility is high, one in which patients suffer from diseases which, if not properly handled, could kill or disable them. A "good" specialty is also one in which the students see a wide variety of diseases so that they are constantly putting to use all of their medical knowledge. Only internal medicine is regarded by everyone as embodying those challenges which make something "really medicine."

To those who know and practice neurology, there is no doubt that it is indeed a "good" specialty. What is needed is a revision in some areas of our undergraduate teaching programs.

Mackay has outlined brilliantly the major philosophic principles of neurologic education:[11]

> Neurologic education must be biologic in its orientation; neurologic education must be complete in its extent; whatever is neurologic belongs to neurology; the point for emphasis here is that in certain places the diagnosis and management of many of these conditions have been lost by the neurologist precisely because instruction of the medical students in these fields has been abandoned to the respective special therapists. To impressionable youth, the disease ceases to be neurologic and becomes medical, pediatric, neurosurgical or orthopedic. Even in neurology, nature abhors a vacuum: neurology may reclaim its own in the teaching of undergraduates and residents. Neurologic education must be clinical in its emphasis; neurology is not an intellectual pastime or an idle philosophy. Like all of medicine, its ultimate function is the diagnosis and treatment of human illness, the understanding of human disease and the alleviation of human suffering. Neurologic education must be therapeutic in its goals; the unthinking reproach often laid upon the neurologist is that he diagnoses but does not treat. True it is that the neurologist deals with the most stubbornly resistant of all diseases. Yet such a reproach is unmerited, and arises partly from the tendency of the neurologist to abandon therapeutically vulnerable diseases to other specialties. It also arises from too narrow a conception of treatment as specific therapy rather than total management. Neurologic education must be progressive in its outlook and point out the rich harvest in our specialty to be reaped by research.

It is undeniable that immense progress has been made in neurology in the past ten years. This must be brought to the attention of medical students as well as the general public. A simple program of orientation about the role and scope of neurology should be introduced by neurologists in their medical school curricula to dispel widespread misconceptions on the part of students. Many of the true facts about neurology are known to students, as is evident from the results of our questionnaire. That they need to be emphasized and expanded can be inferred from the fact that so many neurologic residencies and staff positions remain unfilled.

The author wishes to express his thanks to Alex Sweet, Ph.D., and W. Clarke Wescoe, M.D., for their help and advice.

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Microgyria: a case report

C. G. Smith, M.D., Ph.D., and Eric A. Linell, M.D.

MICROGYRIA is a pathologic finding which indicates defective development of the cerebral cortex. As the term implies, the cerebral hemisphere of 1 or both sides has patches of small, closely crowded gyri which may be badly distorted. The condition is considered uncommon—probably because it is often overlooked. When microgyria is present, some degree of mental slowness occurs and, often, the defective cortex serves as an epileptogenic focus.

The cause of the defective development of the cortex is not known. Possibly, it may have a genetic origin, but defective development may also be due to extraneous influences—such as infection, trauma, and temporary ischemia. Since prevention of microgyria depends upon understanding its cause, each case deserves careful study. The findings in the examination of a patient with microgyria form the basis of this report.

CASE REPORT

A 2-year-old boy, an epileptic from birth, died on the way to the hospital in status epilepticus. No further information is available.

The brain was removed at another hospital and was made available after an elongated block of cortex and adjacent white matter had been removed from the lateral surface of the right temporal lobe (Fig. 2).

Examination of the brain. The brain, of normal size for a 2-year-old child, weighed 1,147 gm. The meninges, the arteries, and the veins were grossly normal. The basal arteries had healthy walls and normal distribution. Considerable generalized venous congestion and small patches of recent subarachnoid hemorrhage from postmortem rupture of veins were present on the lateral surface of the right frontal lobe. The right superficial veins ascending to the superior sagittal sinus penetrated the arachnoid farther from the midline than usual.

The brain stem, cerebellum, and left cerebral hemisphere looked normal. The right hemisphere was smaller than the left (Fig. 1), and the concavity of its orbital surface was abnormally deep. An area of microgyria was seen on the lateral surface of the right hemisphere around the posterior half of the lateral sulcus which involved the posterior half of the temporal lobe. The small convolutions in this area were firmer than elsewhere and were outlined by shallow sulci. Figure 1 demonstrates marked atrophy with outward deviation of the right occipital lobe behind the grossly micro-

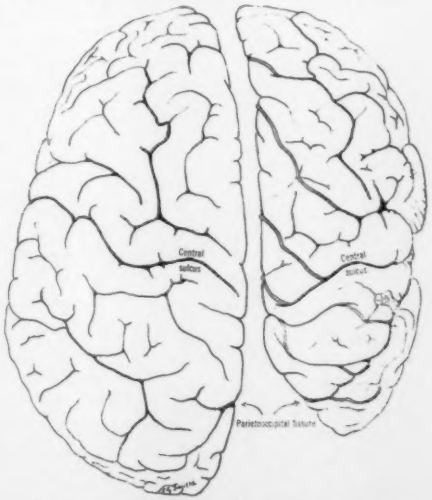

Fig. 1. The superior aspect of the right and left hemispheres: The artery shown in double lines emerging from the right parietooccipital fissure is a branch of the posterior cerebral artery; the other arteries shown in double lines are branches of the right anterior cerebral artery.

From Department of Anatomy and Division of Neuropathology, University of Toronto, Canada.
Read (C.G.S.) before the Cajal Club, American Association of Anatomists, Buffalo, N. Y., April 1, 1958.

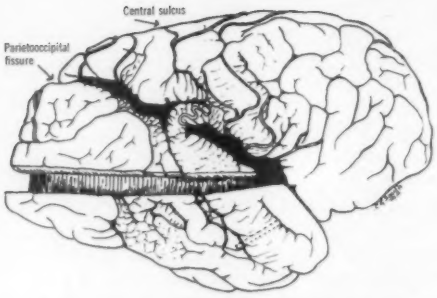

Fig. 2. The lateral aspect of the right hemisphere: A branch of the posterior cerebral artery descends on the occipital lobe from the parietooccipital fissure. Branches of the anterior cerebral artery descend and pass posteriorly to enter [1] the lateral extension of the parietooccipital fissure (see text), [2] the central sulcus, [3] the precentral sulcus, and [4] the superior frontal sulcus. The arteries emerging from the lateral sulcus are branches of the middle cerebral artery. Some of the latter which had been cut could not be traced and are omitted.

Fig. 3. The inferior aspect of the right hemisphere

gyric area. In a horizontal section of the brain that passes through the deeper part of the basal ganglia, cystic degeneration was seen at the posterior end of the lentiform nucleus and in the adjacent posterior limb of the internal capsule. A suggestion of a zone of demyelination occurred in the area of microgyria at the junction between the cortex and white matter, but the deeper white matter was grossly normal. There was slight internal hydrocephalus ex vacuo of the posterior horn of the right lateral ventricle.

The gyri and sulci of the left hemisphere looked normal. Opening the deep sulci revealed no hidden abnormal gyri. The gyri and sulci of the medial surface of the right hemisphere were also normal. On the lateral surface, however, extending on to the inferior surface, a large patch of abnormal gyri was seen (Figs. 2 and 3). The named gyri included in this abnormal area are shown in the diagrams of the sulci and gyri of a normal hemisphere (Figs. 4 and 5).

The characteristics of the area of abnormal gyri are shown to advantage in the anatomically accurate tracings of the lateral and inferior surfaces of the right cerebral hemisphere (Figs. 2 and 3). The lesion gives one the impression that the area involved suffered some form of blight during its development and that the blighted area shriveled and caused distortion of the bordering and grossly normal gyri. The extent of the cortex involved in the lesion was not appreciated until the surrounding sulci were opened up and identified. Then it was evident that a number of gyri had dropped out and their places were occupied by the expansion of the gyri bordering the lesion. The missing gyri were the posterior part of the superior parietal lobule, the angular gyrus of the inferior parietal lobule, and the inferior half of the postcentral gyrus. These gyri were replaced by a deep fissure which extended from the parietooccipital fissure outward toward the end of the lateral sulcus (Fig. 2). The gray matter in the walls of this fissure and on 2 ridges extending obliquely across its floor had a nodular surface. The undulating course of the branch of the middle cerebral artery that crossed the supramarginal gyrus (Fig. 2) further suggested atrophy of the underlying cortex.

The appearance of the surroundings of this microgyric area showed that the right occipital lobe had spread forward to meet the backward growth of the remaining parietal lobe (Fig. 1). However, other evidence of molding was seen.

1] The posterior end of the superior frontal sulcus was farther from the midline than on the left side (Fig. 1).

2] The veins draining into the superior sagittal sinus left the arachnoid at a point farther lateral than usual.

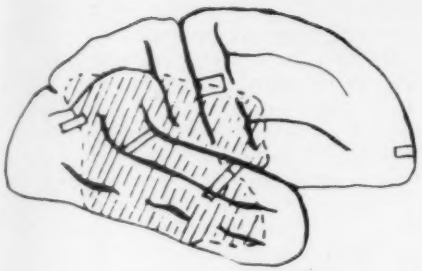

Fig. 4. A diagram of the chief sulci and gyri of the lateral aspect of a normal hemisphere: The shaded area shows the extent of the abnormal gyri pictured in Figure 2. The rectangles locate the samples of cortex examined histologically.

Fig. 5. A diagram of the chief sulci and gyri of the tentorial surface of a normal hemisphere: The shaded area shows the extent of the abnormal gyri pictured in Figure 3.

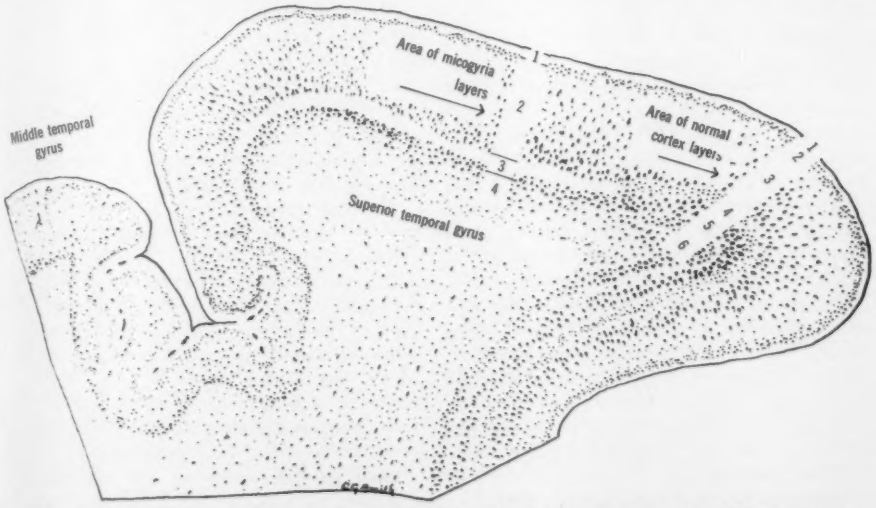

Fig. 6. A low-power drawing of a Nissl-stained section of the superior and middle temporal gyri of the right hemisphere. The section is taken near the temporal pole at the site indicated by the rectangle in Figure 4.

3] The branches of the right anterior cerebral artery supplied a larger part of the lateral surface than normal (double lines in Fig. 1).

4] The inferior half of the precentral gyrus was abnormally wide (Fig. 2).

MICROSCOPIC EXAMINATION

Right hemisphere. Samples of cortex from the sites marked by rectangles in Figures 4 and 5 were examined histologically. These showed that the cortex in the abnormal, distorted gyri had the structural characteristics of microgyria.[1] Sections taken at the line of junction of abnormal and normal gyri, seen grossly, showed that this line corresponded to the transition zone between abnormal and normal cortex. Sections of the frontal pole cortex, calcarine cortex, and hippocampal cortex were normal.

The general structure of the abnormal cortex is illustrated in Fig. 6. This is a drawing made from a section of the right superior and middle temporal gyri at the site marked in Figure 4. The typical 4-layered microgyric cortex is seen at the summit of the gyrus.

These layers of the cortex are numbered from the surface. Layer 1 is a marginal layer, poor in cells, which corresponds to the molecular layer of normal cortex but is a little wider. Layer 2 is a thick layer of cells, the more superficial of which are small and round; the deeper ones are largely pyramidal. The superficial cells are more closely crowded together than the deeper ones. Layer 3 is a sparsely cellular layer which Crome describes as 'occupied mainly by myelinated fibers. This layer is a sharply defined, unstained band in Nissl preparations but, as Crome found, becomes less distinct in the more convoluted regions of the abnormal cortex, and continuous with the white matter where the fourth layer (see below) is wanting.

At the junction with normal cortex, this acellular layer is continuous with the fourth or internal granular layer. Layer 4 of the microgyric cortex consists of pyramidal and irregularly shaped, moderately large cells. It varies in thickness and may be absent in the more convoluted areas of the abnormal cortex. The deep cells of this layer spread apart and extend diffusely into the white matter where most of them become bipolar—like the majority of the numerous heterotopic nerve cells in the white matter. These cells extend deep into the white matter but do not reach the ependymal lining of the lateral ventricle. The ependymal epithelium is normal. However, considerable subependymal gliosis occurs.

The cortex of that part of the microgyric area that has a grossly nodular surface (Fig. 2) was seen as an undulating band in a stained section. This appearance was due to the infolding of the outer pial surface, which, in some parts, affects only the outer part of the thickness of the cortex (Fig. 6). The shallow furrows, which had probably been open originally, were obliterated by the fusion of the nervous tissue in the opposing walls. The plane of fusion can still be recognized by the line of small vessels which apparently are trapped pial vessels.

The steps in the transition from normal cortex to the most abnormal cortex are evident in Figure 6. The first step is the replacement of the internal granular layer of normal cortex by a relatively acellular layer. This converts normal cortex into the 4-layered cortex characteristic of microgyria.[1] The second step is one in which the cell content decreases progressively; the cells take on a more immature form and become irregularly arranged. This loss of cells continues until the fourth layer disappears, permitting the third layer of the microgyric cortex, a fiber layer, to become part of the white matter. Thus, the microgyric cortex is reduced to 2 layers. The third step is the wrinkling of the outer part of the thickness of the cortex. The shallow grooves that result are closed by the fusion of the opposing walls, trapping the fine vessels of the surface network. In this way, the surface becomes nodular. With the appearance of the fine folds, the cell content is greatly reduced and the cells that remain are widely separated and irregularly arranged. Possibly, the folding of the surface is a result of a greater loss of cells in the deeper cortical layers.

Left hemisphere. Samples of cortex taken from the posterior end of the middle frontal gyrus, from the lower lip of the calcarine sulcus, and from the posterior end of the hippocampal gyrus were normal. A surprise finding was the discovery of an area of abnormal cortex at the frontal pole of the apparently normal left hemisphere (Fig. 1). The characteristics of the abnormal cortex here are the same as those described in the severe microgyric cortex of the right hemisphere.

Basal ganglia, midbrain, and medulla oblongata. Sections of the lentiform nucleus looked normal except for the presence of large perivascular spaces. Sections at the level of the superior colliculus were normal. The substantia nigra was not pigmented, since, according to Obersteiner,[2] it does not acquire its pigment until the fourth year of life. The section of the medulla oblongata through the middle of the olive was normal.

DISCUSSION

The gross and histologic findings in this case strongly suggest to the authors that the cortical lesions described were acquired by the in-

fant early in his fetal life. The fact that the greater part of the cortex of his right hemisphere and practically all of his left cerebral cortex had developed normally makes it difficult to accept the word dysgenesis in its meaning of arrest in development. Also, the severity of the microgyric changes varies markedly within the limits of the grossly microgyric area. However, histologic evidence exists that, at one time, the cortex in the microgyric area was better developed and that the degenerative changes which have occurred have been, to some extent at least, progressive.

We know very little about the factors which may have a deleterious effect on the cerebral cortex in utero, but it is accepted that German measles occurring in the first trimester of the mother's pregnancy may produce major deformities in her infant's brain.

One of us (E.A.L.)[3] reported an infant in whom prenatal thrombosis or embolism caused cortical softening which would have produced congenital hemiplegia if the child had survived. Minor disturbances in the fetal circulation may be sufficient to produce localized, possibly anoxic, lesions in cortical tissue. Under hypothermia, it has been noted experimentally that the heart of the fetal lamb misses beats. These misses become more frequent as the hypothermia is increased.

It is, therefore, interesting to speculate that, in the second or third months of this infant's fetal life, his cerebral cortex was patchily damaged by lack of oxygen or glucose or perhaps, positively, by some deleterious chemical circulating in his blood stream for a length of time sufficient to cause irreversible cortical degenerative changes.

Our thanks are due to Dr. S. F. Penny, pathologist of the Toronto East General Hospital, who made this brain available to us for detailed study.

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CASE REPORT

Agenesis of the corpus callosum with associated facial anomalies

William E. Bell, M.D., and Maurice W. Van Allen, M.D.

SINCE Reil's[1] first description of agenesis of the corpus callosum in 1812, many examples of this anomaly have been recorded, but little insight has been gained on the etiology and pathogenesis. Many noxious factors as well as genetic abnormalities of the anlage of the corpus callosum have been considered as agents responsible for this most interesting and variable congenital malformation. However, our present knowledge based on anatomic studies allows for no unitarian concept of etiology.

One might anticipate that analysis of patients with agenesis of the corpus callosum would yield enough neurologic and psychologic data that the contribution of this normally massive commissure to brain function as a whole might be delineated. This reasonable anticipation has not been realized.[2]

The absence of any characteristic pattern of abnormal behavior or even, in some cases, of any abnormality of behavior at all has resulted in failure to establish a constellation of symptoms by which callosal agenesis might be detected. To date, the diagnosis of this condition has been made only at autopsy or after recognition of the typical pneumoencephalographic patterns described by Davidoff and Dyke[3] and Hyndman and Penfield.[4]*

The coexistence of congenital absence of the corpus callosum and other anomalies has been noted. However, the association of this midline defect of the brain with malformation due to defective fusion of the facial structures has been mentioned infrequently.[5-8] Active cell proliferation establishing fusion of the maxilla and the palate from either side nears completion at about the time the corpus callosum is being formed. The possibility that defects in midline fusion in the face occasionally might be associated with defective formation of the corpus callosum is intriguing.

The following case report may be of interest because extensive aplasia of the nose, palate, and maxilla with signs of generalized spasticity led to the suggestion that midline structures of the brain also might be defective. On this basis, a pneumoencephalogram was done.

CASE REPORT

This male infant was seen at the University Hospitals at the age of 2 months. He had been born at another hospital and, at birth, presented multiple facial abnormalities. The weight at birth was 6 lb., 10 oz.; head circumference, 30 cm.; and chest circumference, 33.5 cm. He was the product of a normal pregnancy and an uncomplicated term delivery. The immediate neonatal period was described as uneventful except for difficulty in feeding.

Family History. The mother was 30 years of age and the father, 33. Both were healthy and displayed no apparent deformities. A 2-year-old female sibling was described as having a congenital dislocation of the left hip. Another sibling was normal. Both of the parents had been married previously, and the mother, by her former marriage, had had 3 children, all well and with no external deformities. The father, by previous marriage, had 2 normal sons. A sister of the patient's

*Davidoff and Dyke and Penfield and Hyndman reported simultaneously on the diagnosis of callosal agenesis by air studies. Tr. Am. Neurol. A. 60:181, 182, 1934.

From the Department of Neurology, State University of Iowa College of Medicine, Iowa City.

Fig. 1. Profile of 2-month-old child. The ears are low-set, and preauricular appendages are present. Aplasia of the nose and microcephaly are evident.

Fig. 2. Midline cleft of upper lip, maxilla, and palate. Aplasia of the nose. Eyes are wide-set, and the right orbit appears to be oblique in position.

father had syndactylia. No other congenital deformities in the family had been recognized.

Physical Examination. The child's weight was 9 lb., 12 oz. The head was small, measuring 34 cm. in circumference, while the chest was 37 cm. in circumference. The total body length was 57 cm. The anterior fontanel was open and flat and measured 1 by 1 cm. The occiput was flat. The ears were low-set, and preauricular appendages were present on either side (Fig. 1). The tragus was small bilaterally, and the external auditory canals were large. The nose was absent, and a wide midline cleft of the upper lip extending posteriorly through the hard and soft palate was apparent (Fig. 2). The turbinates and nasal septum were absent. Movement of the tongue was normal, and tonsils and adenoids were present. Both sublingual glands were enlarged, particularly the left. As a result, the tongue was deviated upward and to the right. The infant's eyes were unusually wide-set, and mild proptosis was evident. The right eye was directed obliquely outward. Vision appeared to be present in both eyes. The pupils responded to light. The optic fundi were normal. Examination of the heart, lungs, abdomen, back, and genitalia disclosed no abnormalities. The child was active and playful and had a loud, forceful cry. The extremities were normally developed, but there was generalized hypertonicity and exaggerated activity of the tendon stretch reflexes. Occasionally, the child was observed to assume a position of universal extensor rigidity resembling that of a decerebrate state. The Moro reflex was present.

Laboratory Findings. Hemoglobin was 8.6 gm. per cent; red blood cell count, 2.8 million per cubic millimeter; and white blood cell count, 12,350. Urinalysis was normal. Cerebrospinal fluid protein was 60 mg. per cent, glucose, 46 mg. per cent. Electroencephalo-

Fig. 3. Pneumoencephalogram, lateral view. Agenesis of the corpus callosum. Note high position of third ventricle and attenuation of anterior horns of lateral ventricles.

Fig. 4 Pneumoencephalogram, posteroanterior view. Agenesis of the corpus callosum. Note the midline cleft through the maxillary and nasal regions.

graphic examination showed no gross asymmetry and no spike activity. Due to excessive movement artifact, further interpretation was not possible. Roentgenogram of the chest disclosed no abnormalities of the lungs, heart, or great vessels. Roentgenograms of the skull revealed microcephaly. Cranial sutures were open, but anterior and posterior fontanels were small. The mandible was normal. There was a widely cleft palate and complete absence of nasal bones, nasal septum, and turbinates.

A pneumoencephalographic examination revealed findings typical of complete agenesis of the corpus callosum (Figs. 3 and 4). The lateral ventricles were widely separated with dorsal extension of the third ventricle. The lateral view showed the high position of the third ventricle as well as attenuation of the anterior horns of the lateral ventricles. The often described "bat-wing" appearance of the ventricular system in the anteroposterior projection was obvious (Fig. 5).

Because of extensive deformities and poor neurologic prognosis, reparative surgery of the face was not advised and the child was discharged to a state institution. The final diagnoses were: [1] cleft palate and lip, [2] congenital absence of the nose, [3] microcephaly, [4] agenesis of the corpus callosum and other central nervous system disorder, and [5] anomalies of the external ear including preauricular appendages.

DISCUSSION

Midline clefts of the maxilla and palate as presented by this case are considered rare as contrasted to the more common laterally lying clefts.[9] Many of the embryonic structures contributing to the formation of the face and jaws are clearly evident by the fifth week.[10]

At this time, the frontal process appears as an overhanging prominence in the midline. On either side of this lie the nasal processes, the nasomedial and nasolateral, surrounding the olfactory pits. The maxillary processes of each side grow toward the midline from the lateral angles of the oral cavity. The upper lip, jaw, and nose arise from these primitive structures. In the sixth week, the maxillary processes become larger and continue to grow toward the midline and the nasal processes are approximated. Meanwhile, the medial parts of the nasal processes have enlarged, and the upper jaw is bridged by fusion of the 2 nasomedial processes in the midline and their fusion with the maxillary processes laterally. Failure of fusion of the nasomedial processes in the seventh week will result in a midline cleft of the upper lip and maxilla. As the upper jaw is formed in the seventh and eighth week of the embryo, the palatal shelves make their first appearance. Like the upper jaw, the palate also receives contributions from the nasomedial and maxillary processes. The lateral palatal processes or shelves arise from the maxillary processes and grow toward the midline where they fuse to form the palate and, thus, provide a bridge between the oral and nasal cavities. The nasal septum joins the palate above, thus dividing the nasal cavity. The facial defects in the case reported might be explained by failure of fusion of the nasomedial processes. Failure of fusion of the lateral palatine processes account for the palatal defect.

Fig. 5. Pneumoencephalogram, anteroposterior view. Agenesis of the corpus callosum. There is wide separation of the lateral ventricles, dorsal extension, and dilation of the third ventricle, angular dorsal margins, and concave medial margins of the lateral ventricles.

At the time the formation of the facial structures is being concluded, the early development of the corpus callosum is initiated. The first evidence of the corpus callosum appears in the third fetal month[4] as a thickening of the lamina terminalis. The most anterior aspect of the corpus callosum develops first and extends in a posterior direction carrying the septum pellucidum beneath it. Formation of the corpus callosum, hippocampal commissure, and septum pellucidum occurs contemporaneously and is not complete until the fifth fetal month.

Bruce[11] has indicated that the anatomic pattern of a defect in the corpus callosum will depend upon the fetal age at which arrest of development occurs. If arrest occurs during the first month of embryonic life, complete absence of the corpus callosum, septum pellucidum, and hippocampal and anterior commissures, as well as a single ventricle and fusion of the hemispheres, results. Developmental arrest between the first and fourth fetal months produces absence of the corpus callosum, septum pellucidum, and anterior and hippocampal commissures, but the hemispheres and lateral ventricles will be divided. Arrest occurring after the fourth fetal month results in partial absence of the more posterior portions of the corpus callosum, while the genu will be intact.

Of historic interest is the first report of agenesis of the corpus callosum by Reil[1] in 1812. He described a 30-year-old mentally defective female who died after a fall. On examination of the brain, absence of the middle and posterior portions of the corpus callosum

and the septum pellucidum as well as hydrocephalus was found. Reil's interest in the corpus callosum is indicated by his comments concerning the attenuation of this structure in the kangaroo and its absence in birds. The literature following this initial observation has pointed out the wide variety of associated intracerebral and extracerebral anomalies and the diagnostic criteria by air studies. Guttmann,[12] in 1929, first reported a case of callosal agenesis, in which encephalographic examination had been done. Apparently, the significance of the roentgen findings had not been recognized during life. The diagnosis in this case was made at autopsy. In 1934, Dyke and Davidoff[3] established the following characteristics of agenesis of the corpus callosum as shown by encephalographic examination: [1] marked separation of the lateral ventricles; [2] angular dorsal margins of the lateral ventricles; [3] concave mesial borders of the lateral ventricles; [4] dilation of the caudal portions of the lateral ventricles; [5] elongations of the interventricular foramina; [6] dorsal extension and dilation of the third ventricle; and [7] radial arrangement of the mesial cerebral sulci around the roof of the third ventricle and their extension through the zone usually occupied by the corpus callosum.

Facial anomalies occurring with callosal agenesis and anomalies in other extracranial structures have been described previously.[13] Van Epps[6] reported 12 patients with agenesis of the corpus callosum, 2 of whom had cleft lip and palate. In addition to these defects, 1 displayed hydrocephalus secondary to aqueductal obstruction and neuronal abnormalities of the cortex suggestive of a fetal cortical pattern. The other presented bilateral clubbed feet in addition to the defects in the corpus callosum and face. The child reported by Courville[7] died at 6 weeks. There were cleft lip and palate, microcephaly, and absence of the nasal septum and corpus callosum at autopsy. The cerebrum was found to occupy only the anterior one-third of the cranial vault; the posterior two-thirds was filled by a sac containing fluid. The rhinencephalon and corpus striatum were not seen. Shryock and Knighton[8] described the autopsy findings of a newborn infant with cleft lip and palate, aplasia of the nose, microcephaly, arhinencephaly, agenesis of the corpus callosum and septum pellucidum, and other widespread cerebral malformations. The findings in these cases,[6–8] as well as our own, would seem to correlate with what could be predicted from a study of embryology: when defects of fusion of facial structure are associated with cerebral defects, the latter are apt to be advanced, to involve more than simple callosal agenesis, and to be seriously disabling. In our case, one might reasonably date the defects of fusion of the face from developmental arrest beginning in the seventh week. The arrest of development of cerebral structures probably occurred between the first and fourth fetal months.

The possibility of clinical diagnosis of agenesis of the corpus callosum must await an understanding of the function of the normal structure. However, the association of this anomaly with facial defects probably is more than an occasional coincidence. If so, some basis for a reasonable prediction of the presence of the anomaly may be established. This could be of more than academic interest when surgical judgment concerning the advisability of repair of facial defects is in the balance.

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CASE REPORT

Spontaneous ventriculocisternostomy with relief of obstructive hydrocephalus

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RUPTURE of the ventricular wall in obstructive hydrocephalus has, in some instances, given rise to subpial collections of cerebrospinal fluid producing diverticula.[1–4] Infrequently, the pia is ruptured, resulting in free passage of the cerebrospinal fluid to the subarachnoid space proximal to the ventricular block.[3,5–7] Theoretically, a total ventricular rupture would seem to offer a means of relieving the symptoms of increased intracranial pressure.[8] However, to our knowledge not more than 2 cases of spontaneous regression of such symptoms by this mechanism have appeared in the literature.[5,6] This surprisingly low incidence has prompted us to report a case of obstruction of the fourth ventricle with an established short circuit for the cerebrospinal fluid from the third ventricle to the superior cistern.

CASE REPORT

The patient, a 16-year-old boy, was admitted to the Surgical Department of Ullevaal Hospital as an emergency case on April 10, 1957. He was sent there from a local school for the blind with a note stating that in 1955 he was diagnosed as suffering from an inoperable brain stem tumor. He now was complaining of abdominal pain. It was noted that he had no headache. On admission, abdominal examination revealed no abnormalities. Neurologic examination revealed bilateral optic atrophy, nystagmus, and a mild right sided hemiparesis. Soon after admission, the patient suddenly stopped breathing, became cyanotic, and lapsed into coma. He was intubated and given artificial respiration. In the absence of any detailed information about his illness and after consideration of the clinical picture as it was on admission, ventricular puncture seemed indicated. This was performed through two burholes in the frontal region; 70 cc. of cerebrospinal fluid was removed, and a limited ventriculogram was performed. During the procedure, spontaneous respiration and consciousness returned, and the patient remained relatively well for five to six hours. He subsequently suffered from unexplained generalized convulsions and expired.

Autopsy Findings. A postmortem examination was performed the next day. External examination of the formalin-fixed brain revealed a conglomerate of cysts on the left side of the medulla oblongata in the cerebellopontine angle. The pons was rostrally dislocated, and the medulla oblongata was tremendously increased in thickness, up to a diameter of approximately 3.5 cm. The third ventricular floor bulged into the interpeduncular fossa (Fig. 1).

Coronal sections of the brain revealed on the left side of the medulla oblongata a round, circumscribed, partly necrotic tumor mass, measuring 2.5 cm. in maximum diameter. The rest of the brain stem showed a more diffuse tumor infiltration with multiple cystic spaces. One of the cysts was on the surface of the brain stem in the left cerebellopontine angle (Fig. 1). Another large cyst arose on the left side from the floor of the fourth ventricle and bulged into the ventricular lumen, thereby obliterating it (Fig. 2). The lateral ventricles were only slightly dilated, while the third

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Fig. 1. The surface of the unfixed brain from the ventral aspect. Note the cysts on the left side of the bulb, the displacement of the pons and medulla oblongata, and the bulging of the third ventricular floor into the interpeduncular fossa.

Fig. 2. The cyst which obliterated the fourth ventricle. Cut surface of the formalin-fixed pons and cerebellum as seen from the caudal aspect. The remnants of the ventricular lumen on both sides of the cyst were only potential spaces due to the high pressure of the cyst fluid.

ventricle and the aqueduct were moderately so (Fig. 3). There was an irregular rupture in the suprapineal recess of the third ventricle which could have been taken for an artifact, were it not that the superior cistern showed a considerable dilation which had resulted in a bilateral elevation of the floor of the lateral ventricles (Fig. 3). This phenomenon was considered as a true demonstration of an established intra vitam communication between the ventricle and the cistern.

Microscopic Examinations. The tumor mass in the medulla was diagnosed as a spongioblastoma polare. Fibrillary astrocytes constituted the main portion of the cyst walls. The pons exhibited a diffuse gliosis with fibrillary astrocytes and gemistocytes as the principal cell components. The edges of the ruptured suprapineal recess were likewise heavily gliotic.

The unusual finding of a patent rupture of the third ventricle in association with a tumor obstructing the fourth ventricle made us look into the patient's earlier records from the Rikshospital, Oslo, and from Sarpsborg City Hospital, where he had spent the last three years of his life.

The illness started suddenly in April 1950 with severe headache, nausea, vomiting, fever, and neck rigidity. It was diagnosed as meningism, treated at home with some tablets, and "cured" in three weeks' time. Soon after, the patient was noted to be dragging his right foot and later was found to be somewhat weaker in his right hand. In the interim, he continued to complain of intermittent headache and had nausea and vomiting, especially in the morning. In December 1951, he was referred to the Neurological Department of the Rikshospital. After various examinations, he was diagnosed as suffering from postencephalitic spastic hemiparesis and sent home. In April 1954, he was admitted to Sarpsborg Children's Home. From there he returned to the Rikshospital for neurologic evaluation on March 28, 1955, being completely confined to bed with persistent headache, nausea, vomiting, dizziness, and so on. Various examinations suggested the presence of an infiltrating tumor of the brain stem, which was considered to be inoperable. Deep x-ray therapy was attempted on two days but had to be discontinued as it made the patient both

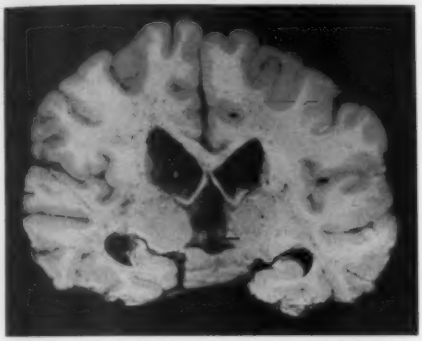

Fig. 3. Coronal section of the formalin-fixed cerebral hemispheres and midbrain. Note the rupture in the suprapineal recess and the dilation of the superior cistern.

subjectively and objectively worse. He then was transferred to Sarpsborg City Hospital as a nursing case. After one year of a complete invalidism with persistent headache, intense dizziness, and a practically complete hemiparesis, his symptoms spontaneously regressed. In a matter of a few weeks, he gradually left his bed and became symptom free. His neurologic defects also regressed. He then was transferred to the home for the blind for occupational therapy, from which he was admitted to this hospital. During his stay in the home for the blind, he had no headache, though now and again he complained of abdominal discomfort and anorexia.

A comparison of the ventriculograms made in March 1955 and April 1957 revealed no progression of the hydrocephalus during the two-year interval. However, the latter ventriculogram showed a continuity of the air shadow of the third ventricle with that of the superior cistern. This finding was not present two years earlier (Figs. 4 and 5).

DISCUSSION

The clinical course of the patient's illness leaves no doubt that a change in the dynamics of the cerebrospinal fluid flow occurred between April and August 1956. This was demonstrated by a complete disappearance of the subjective symptoms and a regression and complete disappearance of the objective neurologic findings of cranial nerve paralysis, hemiparesis, and hemianesthesia. The postmortem examination conclusively excluded the possibility of a regression of the disease itself. The brain stem tumor was found to be completely obliterating the fourth ventricle (Fig. 2), but the ventricular system proximal to the obstruction was dilated surprisingly little. It seems fairly certain to us that the rupture in the posterior wall of the third ventricle, seen at the postmortem examination, must be re-

Fig. 4. Air encephalogram in March 1955 showing the outline of the third ventricle, aqueduct, and the fourth ventricle. Note the presence of slight dilation of the suprapineal recess.

Fig. 5. Ventriculogram in April 1957 outlining the third ventricle. Note the continuity of the air shadow of the third ventricle (arrows) with that of the superior cistern. The fourth ventricle is not filled.

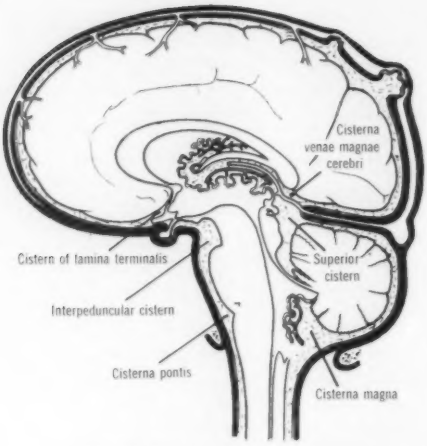

Fig. 6. The subarachnoid cisterns

sponsible for providing a short circuit for the cerebrospinal fluid from the third ventricle to the subarachnoid space. The effect of such a rupture can be easily understood by referring to Figure 6 which shows the normal cerebrospinal fluid pathways. In view of the variable terminology in the literature, the various cisterns are labeled in the diagram to clarify the nomenclature used here. The cisterna ambiens is not labeled in the diagram. We restrict this term to that part of the subarachnoid space which surrounds the cerebral peduncles (parapeduncular cistern), reserving the name superior cistern for the part that is dorsal to the quadrigeminal plate.

It should be pointed out that Dandy's[9] third ventriculostomy and Torkildsen's[10] ventriculocisternostomy, devised to relieve the symptoms of obstructive hydrocephalus, were based on the same principle of producing a direct communication between the ventricular system proximal to the obstruction and one of the subarachnoid cisterns.

Dandy[9] advocated the creation of an opening in the anterior wall of the third ventricle communicating it to the cistern of lamina terminalis. Successful surgical treatment of obstructive hydrocephalus according to a similar technic has been reported recently by Cohen[11] and Scarff.[12] The benefit of a spontaneous rupture of the lamina terminalis was demonstrated in a case reported by Sweet.[6] His patient, a 54-year-old woman, experienced spontaneous relief of increased intracranial pressure of three years' duration. She remained symptom-free for nine years, when she died due to direct involvement of the vital centers by her increasing midline cerebellar tumor. A patent opening in the lamina terminalis was disclosed on postmortem examination of the brain specimen.

By using a rubber tube, Torkildsen[10] created a shunt between one of the lateral ventricles and the cisterna magna in a number of patients suffering from obstructive hydrocephalus. Though technically different, a similar principle was successfully utilized by Macfarlane and Falconer,[13] who treated a case of obstructive hydrocephalus by producing a communication between a diverticulum of one of the lateral ventricles and the cisterna ambiens.

Several authors have drawn attention to the enlarged suprapineal recess in cases of obstructive hydrocephalus. Considering the frequency of such a dilation of the suprapineal recess, it is surprising that a review of the literature reveals only 4 cases of actual rupture at this site (2 cases each by Torkildsen[7] and Kajtor and Haberland[3]). However, no relief of increased intracranial pressure was observed in these cases. Lack of improvement may be due to a need for a certain interval of time to establish equilibrium in the new cerebrospinal fluid dynamics. This suggestion was put forth by Torkildsen[10] to account for the delay in improvement following ventriculocisternostomy. If these 4 patients had lived longer, they might have benefited from the spontaneous ventricular rupture. This view is supported by the gradual improvement in signs and symptoms observed in our case.

Besides the patient reported by Sweet,[6] the only other case of relief of increased intracranial pressure due to spontaneous rupture of the ventricular wall was reported by de Lange.[5] His patient, a child whose head measured 73 cm. at the age of 5½ months, showed a spontaneous regression to 51 cm. at the time of his death seventeen months later. On postmortem examination, he was found to have a dorsolaterally directed channel from each lateral ventricle; the right one

reached the surface of the cerebral hemisphere and was thought to provide the alternative pathway for the cerebrospinal fluid.

From the introductory remarks, the most common sequence of a ventricular rupture appears to be the establishment of extracerebral pial diverticula containing cerebrospinal fluid.[1–4] Whether this results from higher resistance of the pia to the distending forces cannot be decided. The site of predilection for pial diverticula is the collateral trigone of the lateral ventricles between the forward sweeping crus of the fornix and the forceps major of the corpus callosum. None of the reported cases of diverticula at this site manifested any spontaneous improvement in the patient's condition. However, the surgically produced communication[13] between such a diverticulum and the cisterna ambiens resulted in a substantial regression of the pressure symptoms.

SUMMARY AND CONCLUSIONS

1] A case is reported of spontaneous relief of increased intracranial pressure as a result of rupture of the suprapineal recess of the third ventricle into the superior cistern.

2] A survey of the pertinent literature revealed only 2 cases of spontaneous relief of increased intracranial pressure due to a rupture in the ventricular system. One of these exhibited an opening in the lamina terminalis, and the other had a ruptured diverticulum from one of the lateral ventricles to the surface of the cerebral hemisphere.

3] The spontaneous recovery in the reported case was found to be gradual. This might explain the lack of improvement in 4 otherwise similar cases reported in the literature.

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CASE REPORT

Listeria septicemia and meningitis in a case of lupus erythematosus

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BEFORE 1953, meningitis caused by Listeria monocytogenes was considered very rare. Only about 40 cases had been reported in the world medical literature. Since then, however, cases have been recorded with greater frequency.

The organism was first identified in 1925 by Murray, Webb, and Swann[1] and was called Bacterium monocytogenes because of the marked monocytosis occurring in their infected rabbits. The first human patient with listeriosis was reported in 1921.[2] The causative organisms, erroneously called diphtheroids, were fortunately preserved in the Pasteur Institute and, many years later, proved to be L. monocytogenes.[3] In 1936, Burn first associated the organism with a case of meningitis.[4]

Although excellent reviews of listeriosis have been published,[5,6] we are presenting the following case of Listeria septicemia and meningitis because of the rare association with disseminated lupus erythematosus.

CASE REPORT

A 48-year-old stenographer was admitted to Montefiore Hospital on October 31, 1957. She had had weakness, fever, severe headaches, frequent emesis, and drowsiness for three days.

In 1952, she had begun to have pain in the joints of her fingers, knees, ankles, and lower back and swelling of her hands, ankles, and periorbital areas. A diagnosis of disseminated lupus erythematosus was made in 1953. At that time, studies of her blood revealed anemia, leukopenia, hemolysis, and lupus erythematosus cells. During continuous treatment with adrenal cortical steroids, her hemoglobin level rose, but she continued to have intermittent episodes of joint pain and fever. She also had skin rashes of the lower extremities, ulcerative stomatitis, and an episode of lobar pneumonia.

Physical examination at the time of admission revealed her to be acutely ill, well developed, and obese. She had crackling rales at the right lung base. A Grade II blowing systolic murmur was best heard at the cardiac base and left sternal border. The tendon reflexes were absent, and a right Babinski response was present.

The temperature was 104° F.; blood pressure, 150/90; and pulse, 100.

The white cell count was 4,000 with 70% neutrophils, 7% band cells, 20% lymphocytes, and 3% eosinophils. The hematocrit was 45%. Urinalysis and nose and throat cultures were unremarkable. No roentgenographic evidence of pneumonia was seen.

Bacteriologic studies were made from 2 blood specimens. Treatment was begun with 2,000,000 units of penicillin and 2 gm. of streptomycin daily. She was also given intravenous fluids, 40 units of ACTH on admission, and 7.5 mg. of prednisone. On the third hospital day, another blood specimen was taken and 200 mg. of Solu-Cortef daily was added.

Her temperature remained between 101 and 104.8° F., with a proportionately elevated pulse. Her stools became watery, and she perspired profusely. During the fifth day, she became semicomatose and developed nuchal rigidity and rapid respirations. Her eyes deviated to the right, and Kernig's sign was elicited. A lumbar puncture revealed the cerebrospinal fluid to be slightly cloudy, with a pressure of 280 mm. The fluid contained 29 red

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cells and 548 white cells per cubic millimeter. She was given sulfadiazine and Chloromycetin.

On the sixth day, right facial paresis appeared, and respirations became stertorous. She died during an emergency tracheotomy. Permission for autopsy was refused.

BACTERIOLOGIC STUDIES

Deep beta hemolytic colonies of L. monocytogenes were observed on the third day of incubation at 37° C. of the 2 blood specimens obtained before the start of antimicrobials.

Gram stains of the young, actively growing cultures revealed small, gram-positive bacilli with rounded ends arranged singly, in pairs, short chains, V shapes, and palisades similar to the morphology of the diphtheroid bacilli. The organisms were nonsporulating and were not acid fast. Motility was sluggish and tumbling-type in four- to five-hour broth cultures.

Thioglycollate subcultures showed gram-positive thread forms which represented the rough stage of the organism.

Although organisms were not identified in the direct smear of the cerebrospinal fluid, they were recovered from this material after four days' incubation and were found to be identical to those obtained in blood culture.

BIOCHEMICAL REACTIONS

Dextrose, maltose, salicin, and trehalose were readily fermented, while rhamnose showed fermentation after five to six days. Acid without gas was produced in all fermented sugars. During a fourteen-day incubation period, lactose, sucrose, mannitol, dulcitol, xylose, and sorbitol were not fermented. Gelatin was not liquefied, nor was indole produced.

ANTIBACTERIAL SENSITIVITY STUDIES

In vitro sensitivity studies by the disk method revealed the organisms to be inhibited by Achromycin, bacitracin, Aureomycin, Terramycin, Albamycin, neomycin, Ilotycin, Magnamycin, Furadantin, and streptomycin. The organisms were less sensitive to penicillin and were resistant to Gantrisin, polymyxin, and Chloromycetin.

ANIMAL PATHOGENICITY STUDIES

Each of 2 white mice, inoculated intraperitoneally with 0.25 cc. of a twenty-four-hour broth culture, died in less than twenty-four hours. L. monocytogenes was recovered from cultures of the heart's blood, peritoneum, and brain. Microscopic focal areas of necrosis containing rod-shaped bacteria were found in the histologic preparations of the liver and spleen.

Inoculation of the right conjunctiva of a healthy rabbit with 1 drop of a twenty-four-hour broth culture, (Anton's test[7]) resulted in a purulent right conjunctivitis on the third day and a keratitis on the eighth. Listeria organisms were recovered only from the right eye.

Another rabbit was inoculated intravenously with 0.5 cc. of a twenty-four hour broth culture. The animal developed lethargy, diarrhea, nuchal rigidity, and myoclonic movements and died on the fourth day. During that period, the white cell count increased from 5,200, with 3% monocytes, to 28,500, with 60% monocytes. Pure cultures of L. monocytogenes were obtained from the heart's blood and the brain.

DISCUSSION

The only similar case of which we are aware was reported in 1953 by Schulze, Wahle, and White.[8] They cited a rapidly fatal case of Listeria meningitis in a 19-year-old girl in whom a diagnosis of disseminated lupus erythematosus was made two months earlier. She was treated with streptomycin.

Intercurrent infection remains a frequent problem in individuals with disseminated lupus erythematosus. A bacterial diagnosis could not be established earlier in our patient because of the relatively slow growth (three days) of the organism in culture. Septicemia was present before the clinical diagnosis of meningitis was obvious. While no organisms were cultured from blood taken twenty-four hours after initial penicillin and streptomycin therapy, the patient showed no clinical improvement and cultures of the spinal fluid taken on the fifth day revealed Listeria. As in other overwhelming infectious processes, the adrenocortical compounds, when not given with adequate doses of specific antimicrobial drugs, may reduce host resistance to bacterial pathogens.

Judging from previously reported cases, streptomycin does not appear to control Listeria infections and may promote the appearance of resistant organisms.[9] Penicillin, when used alone, is also not very effective.[10]

Clinical experience with listeriosis has indicated that the tetracycline antibiotics are the most efficacious therapeutic agents. Penicillin given with a sulfonamide is also effective, and chloramphenicol is at times of value.

The epidemiologic features of our case are obscure. While transmission of the organism from animal to man[11,12] and, possibly, man to man[13,14] may occur, most of the reported cases have been sporadic and a history of contact with animals, their products, or excreta can often not be elicited.

Purulent meningitis, with or without encephalitis, and septicemia are the most common forms of listeriosis reported in adults. In the human fetus, however, Listeria infection can cause granulomatous cerebral lesions (granulomatosis infantiseptica) resulting in abortion, premature delivery, or a usually fatal septicemia with numerous areas of focal necrosis (listeriomas), especially in the liver.[15] The mothers are seldom ill.[16] Listeria infection may also result in a benign febrile illness which, at times, may closely simulate infectious mononucleosis. In these instances, it rarely causes a significant Paul-Bunnell heterophil agglutination titer but usually results in a high titer of Listeria agglutinins.[6] The organism has also been reported as a rare cause of bacterial endocarditis,[17,18] polyserositis,[6,19] granulomatous conjunctivitis,[12] and urethritis.[13]

No clinical features occurred in our case which differentiated it from meningitides caused by other organisms. The diagnosis rested on the recovery of L. monocytogenes from the blood and cerebrospinal fluid. Serologic studies, which were not immediately available to us, may aid diagnosis if high O and H titers are present,[20] especially when the complement fixation test is also positive.[6]

Although postmortem studies of our patient were not obtained, one would expect to have found evidence of suppurative meningitis. Other necropsy findings reported in this disease have included multiple listeriomas in the parenchymatous organs, carditis, pneumonitis, pleural empyema, splenomegaly, polyserositis, metritis, and rectal and esophageal ulcers.

In general, the prognosis in uncomplicated Listeria meningitis appears to be good. Some individuals who recovered had a prolonged convalescence, and a few developed psychiatric disturbances[21] or neurologic sequelae which included hydrocephalus in infants,[14,22] eyelid ptosis,[23] and paralysis agitans.[19] Death, if it occurs, is usually within a week after onset.

ACKNOWLEDGMENTS

We wish to express our appreciation to Dr. Kurt Elias, the patient's attending physician, for permission to study and report this case, and to Dr. Alfred Cohn, former head of the Department of Bacteriology of the Laboratory Division, Montefiore Hospital.

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Neurology

BOOK REVIEWS

Textbook of Neurology

by H. Houston Merritt, 2d ed., 765 pp., ill., Philadelphia, Lea & Febiger, 1959. $12.50

This is a textbook and guide for medical students, interns, resident physicians, and general practitioners in need of quick reference aid in diagnosis. It covers in sufficient detail the common neurologic disorders and includes succinct descriptions of all the less common disorders.

The author has wisely refrained from using fancy language, and, in simple descriptive terms, he presents the symptoms, the neurologic findings, the etiologic factors, and the pathologic-anatomic changes in the nervous system.

Treatment is covered adequately—and conservatively when the nature of the disease demands it. All practitioners treating patients with multiple sclerosis should read the information on therapy for that disease in order to be fortified with the knowledge of the failures of the past.

It is assumed that the author deliberately did not include the neurophysiologic mechanisms—provided by the experimental neurologist during recent years—to explain the various hyperkinetic disorders so puzzling to students and those unfamiliar with the progress in this important field. This may be disappointing to educators who are attempting to teach neurophysiology and clinical neurology as an integrated subject and to students who want to know the whys and wherefores of unusual symptoms.

The investigator in functional neuroanatomy has done much to dispel the mystery that has surrounded many neurologic syndromes. This basic knowledge has strengthened the position of the clinical neurologist. It would seem feasible, if not imperative, to describe some of the mechanisms underlying tremors, dystonia, spasticity, rigidity, and so on for the better understanding of certain disorders so often ascribed to hysteria.

The material in this text has been well organized and well presented in intelligible language. The book is up-to-date, and the illustrations are unusually fine.

M. G. M

Ciba Foundation Symposium on the Biosynthesis of Terpenes and Sterols

Edited by G. E. W. Wolstenholme and M. O'Connor, 311 pp., Little, Brown and Co., Boston, 1959. $8.75

The title of this volume is somewhat deceptive. The 17 papers and discussions published from the Ciba Foundation Symposium held in May 1958 are principally concerned with important, recent advances in the field of cholesterol biosynthesis and metabolism. As is customary at these special Ciba Symopsia, the participants were all experts in the field and the presentations and discussions are at a fairly technical level. Nevertheless, the neurologic scientist will find in this volume a great deal that is very relevant to his own field, not only because cholesterol is a major constituent

of neural lipids but because of its association with atherosclerosis and the obvious implications for cerebrovascular diseases.

It is clear from the papers in this volume that the steps in biosynthesis of cholesterol are near to complete elucidation. The sequence from acetate via acetyl-coenzyme A and acetoacetyl-coenzyme A to β-hydroxy-β-methylglutaryl-coenzyme A (HMG-CoA) and from there to mevaldic acid and mevalonic acid (MVA) seems to be generally agreed upon. MVA is now recognized as the immediate precursor of the 5-carbon isoprene unit which is polymerized to squalene, the immediate precursor of cholesterol. The paper by Folkers and associates, recounting the discovery and recognition of the significance of mevalonic acid, is a valuable inclusion in the Symposium. Papers by Bucher and Popjak indicate that, in liver, it is primarily the microsomal fraction of cells, supplemented by the supernatant (soluble) fraction, which effects cholesterol synthesis.

No studies on neural tissues were reported at the Symposium, so that it is not yet possible to relate the data except by analogy. The question of what factor or factors affect the rate at which neural cholesterol is turned over in neonatal brains, as compared to adult brains, is not touched on either. However, the alternate pathways for metabolism of HMG-CoA, discussed by Rudney, and the dependence of the HMG-CoA to MVA conversion on triphosphopyridine nucleotide (TPN)-generating systems, outlined by Lynen, would seem to be pertinent observations.

Throughout the Symposium, an awareness of the atherosclerosis problem was readily apparent. Both Bucher and Rudney discussed steps in the biosynthetic sequence at which physiologic controls seemed most likely to be operative. The relevance of these aspects was perhaps best emphasized by Bergstrom's discussion of cholesterol turnover in man as it relates principally to bile acid formation and metabolism. Figure 16 in Bergstrom's paper is particularly instructive. He estimated dietary intake to be about 0.5 gm. of cholesterol per day, whereas some 1.2 gm. per day is excreted as such or as bile acids, a bile acid circulation of 20 to 30 gm. per day occurs, and a cholesterol pool in blood and liver of some 15 gm. is maintained by liver synthesis of 1 to 15 gm. per day. These data underscore the importance of understanding the biosynthetic processes and their controls within the body, especially when considered in the context of atherosclerosis.

A number of other papers in this volume cover interesting related topics, notably vitamin D, the carotenoids (vitamins A and K precursors), and the role of sterols and terpenes in various plant species. Altogether, this Symposium volume is highly recommended for those who wish to keep abreast of the many important developments in this field.

D. B. T.

Amino Acids and Peptides with Antimetabolic Activity

edited by G. E. W. Wolstenholme and Cecilia M. O'Connor, 286 pp., ill., Little, Brown & Co., Boston, 1958. $8.75

This book contains the 17 papers and full discussions by 30 participants in a Ciba Foundation symposium in March 1958 under the chairmanship of Dr. F. Bergel.

The symposium deals with amino acids, amino acid derivatives, peptides and peptide-like compounds which have toxic, cytotoxic, or antimetabolic characteristics. These agents are considered in the context of antimicrobial and antitumor agents.

The proceedings encompass 4 aspects: the chemistry of the compounds including synthetic, structural, and physicochemical facets; their biochemistry in terms of mechanisms of action and biosynthesis; the biology and experimental pathology with respect to problems of structure-activity relationships and to differences between antimicrobial and antitumor agents; and, finally, clinical aspects.

As with most of the Ciba Foundation Symposia, the book is at a highly technical level and presupposes considerable familiarity with the field under discussion—especially the organic chemistry and physical chemistry involved.

For the neurologic scientist, a casual perusal is apt to be disappointing. The nervous system is scarcely mentioned; brief, specific references are found on pp. 69, 148, and 195. However,

the subjects so expertly propounded do have several very important implications for the nervous system and for those interested in various aspects of its chemistry and chemical function.

Of most immediate importance is the fact that a distressingly high proportion of agents belonging to the antimicrobial and antitumor classes of compounds discussed here have significant toxic effects on the nervous system. This fact is of concern not only to the experimental therapist but also to the neurologist. Of more far reaching importance are the several applications of data and principles to neuronal structure and function. Many of the agents or classes of compounds affect one or more of the following cell components: the purine or pyrimidine precursors of nucleotides, the nucleic acids (RNA and DNA), cell-wall structure, and, perhaps, even protein structure itself. Obviously, these are components of particular importance to the neuron. One can project the findings and problems discussed here to such facets of the neuron—in terms of tools for their investigation as well as in principles of synthesis, maintenance, and function.

In addition, the inquiring scientist will find much that is stimulating in this volume. The structures of a number of agents—actinomycins, gramicidins, bacitracins, and so on—and the methods of deducing structure and of laboratory syntheses are covered in considerable detail and have obvious bearing on other peptides—insulin, pituitary hormones, and so on—of more general biologic interest.

The paper by Gale on mode of action of chloramphenicol as a probable block at some stage in nucleoprotein synthesis has many implications. Similarly, the papers by Reilly and by Buchanan on the effects of azaserine and other compounds on purine biosynthesis deserve special attention. The discussion by Abraham and Newton of studies on cell-wall synthesis and the role of uridine nucleotides and neuraminic acid-type compounds is especially pertinent to several fundamental aspects of the neuron and its function. Neurochemists should be most interested in the paper by Brenner on aminoacyl insertion reactions—undoubtedly a very important new concept in peptide rearrangements—and in the papers by Schwyzer on cyclic polypeptides and by Rydon on disulfide cross-linking in peptides.

Everyone, regardless of background or interest, should read the discussions on pp. 86-88 and pp. 269-273 to gain an illuminating insight into the problems and philosophic soul-searching which these experts in the fields of antitumor research are experiencing. One wonders, especially in relation to the latter citation, whether the relatively general neglect of neural tissue and, more particularly, of the neuron itself in such studies may not have been unfortunate. If Farber's suggestion that what is wanted is an agent which would mature the malignant cells and place them back in the normal body economy is to be implemented, perhaps the one cell in the body which has developed this property of maturity most highly, the neuron, could provide real assistance. For those in neurologic sciences who wish to broaden their outlook and to gain some concept of developments which are already affecting their own fields, this volume is recommended. It is not likely to be easy reading for many, but it will be well worthwhile.

D. B. T.

Les Maladies Nerveuses

by A. Van Gehuchten, seventh edition revised and brought to date by Dr. Paul Van Gehuchten, 815 pp., ill., Librairie Universitaire, Louvain, 1958.

This classic textbook of neurology by the late A. Van Gehuchten, whose work constitutes one of the capital pillars upon which the anatomic neurology of post-Charcot period was reared, now represents a historic document rather than a manual of neurology for students and practitioners of our time. Yet, during the period from about 1900 to World War I and even later, Van Gehuchten's 2 volumes of the *Anatomie du Système Nerveux de l'Homme* and their later companion, *Les Maladies Nerveuses*, were the swaddling bands for budding neurologists throughout Europe.

The distinctive feature of the textbook, which made it so widely used, was that it codified with superlative clarity, simplicity, and preciseness of statement the perennially valid

anatomicoclinical facts and fundamental theoretic propositions of neurology at the turn of the century. These facts and propositions remain unchallengable to this time. In the course of more than half a century, these perennial verities have become overgrown, as it were, by new facts and propositions of technologic and conceptual order.

With filial piety, Dr. Paul Van Gehuchten, professor of neurology at the University of Louvain, revised the textbook and incorporated in the original exposition of the anatomicoclinical pathology of the nervous system the advances made in the course of recent years, particularly in neurosurgery and electroencephalography. The book consists essentially of 3 parts: a review of the physiologic anatomy of the nervous system and of the methods of neurologic examination; a syndromatic outline of the classic organic diseases of the peripheral nerves, muscles, and central nervous system; and the functional diseases, including hysteria and traumatic neurosis.

In the revision, the original textbook has lost somewhat the pristine originality of structure and content. As a textbook intended for students and practitioners, it would probably be of limited interest now outside the French-speaking countries. However, it contains much valuable didactic material for an instructor, especially with regard to schemata of anatomicoclinical correlations.

P. I. Y.

"Allergic" Encephalomyelitis

edited by Marian W. Kies, Ph.D., and Ellsworth C. Alvord, Jr., M.D., 576 pp., ill., Charles C Thomas, Springfield, Ill., 1959. $13.50

This detailed symposium, held in October 1957 under the sponsorship of the National Institute of Neurological Diseases and Blindness, comes close to achieving its aim—to gather and collate the available information on the provocative topic of "allergic" encephalomyelitis. The interest which this phenomenon has excited in investigators during the past twenty years is reflected not only in the length of the symposium but also in the large number (59) of contributors. The roster of active participants is too long to enumerate, but the list includes practically all of the pioneers and leading investigators in this field of research from the United States and a number from abroad as well.

The discussion is organized around 4 main themes: 1] An analysis of the histopathology of the lesions, including the manifold variations dependent upon species and individual differences in the experimental animals, differences in the composition of the inoculum, and differences in environment. This aspect of the subject is handled by neuropathologists.

2] The fractionation and identification of encephalitogenic materials with the all important goal of antigen purification. Here the biochemists lead the discussion.

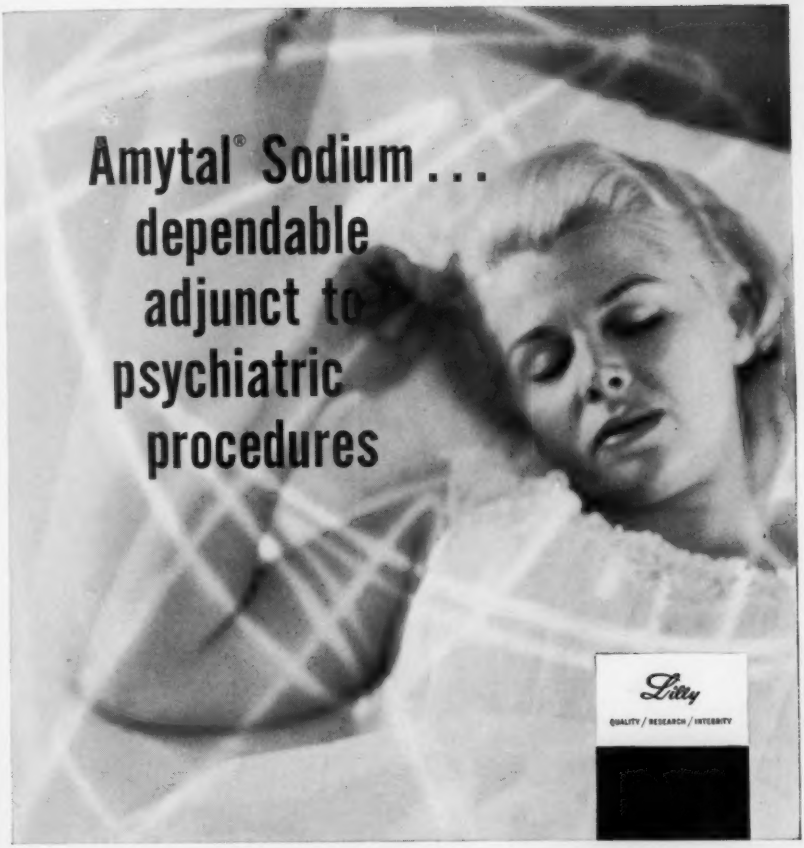
3] A consideration of the possible and probable immune mechanisms involved, including an analysis of the role of adjuvants. This part of the colloquium is conducted, of course, mainly by immunologists. It is this convergence of differing but equally appropriate talents and viewpoints upon a highly complicated biologic phenomenon that gives the book its greatest value and interest.

4] Finally, there is a general preoccupation with relating the purely experimental and highly artificial event of experimental allergic encephalomyelitis with other more or less natural disease states in animals and man, above all with multiple sclerosis. Since the key word "allergic" still has to be placed in quotation marks in the title of the book, it is evident that the most important answers are not yet in. But it can be said that this symposium is a highly informed presentation of our ignorance.

In the informal discussion which makes up a large part of the book is a great deal of shop talk among experts. As is inevitable under these circumstances, a goodly amount of disagreement and even hair splitting follows. This, together with the rather highly specialized nature of the topic, gives the book a limited appeal but by no means an unimportant one. It seems safe to predict that this volume will be a *vade mecum* for all investigators in the field at least for several years to come.

The book is well edited and well printed, and the illustrations are excellent. The useful index, so often lacking in published symposia, will be appreciated by all readers of the book.

R. B. B.



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2. Smith, Richard T.: New York Med. 8:16, 1952.

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NEWSLETTER

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OCTOBER 1959

Deadline for Next Weir Mitchell Award Arnold P. Friedman, Chairman of the AAN Committee on the S. Weir Mitchell Award, announces that the deadline for receipt of manuscripts for this award is January 1, 1960. This award, named in honor of Silas Weir Mitchell (1829 - 1914), a pioneer of American neurology, and sponsored by the AAN Women's Auxiliary, is made annually to the AAN junior member in neurologic training who submits the best unpublished essay on a problem in basic or clinical research in any aspect of neurology. The award carries a Certificate of Award, a cash honorarium of $200, and free transportation for the recipient to the next annual Academy meeting, to be held at the Eden Roc Hotel in Miami Beach (April 25-30, 1960). The recipient of the award will read his paper at the opening of the general scientific sessions of this meeting. The Academy reserves the right to publish the selected manuscript.... Manuscripts must be written by a single author, must be typewritten, double spaced, and submitted in quadruplicate to Mrs. J. C. McKinley, Executive Secretary, American Academy of Neurology, 4307 East 50th Street, Minneapolis 17.

American EEG Society Elects New Officers At their annual June 1959 meeting in Atlantic City, the American Electroencephalographic Society elected Arthur A. Ward, Jr., President; Jerome K. Merlis, President-Elect; George A. Ulett, Secretary; and Isadore S. Zfass, Treasurer. Inquiries and communications should be sent to Doctor George Ulett, Secretary, American EEG Society, Research Laboratories, Washington University School of Medicine, St. Louis 4.

Association of British Neurologists Becomes Official Body to the WFN Macdonald Critchley, Vice-President of the World Federation of Neurology and official delegate to the WFN, announces that the Association of British Neurologists is to be considered the official body to represent the United Kingdom in the World Federation of Neurology. The Association of British Neurologists has also appointed Doctor William Gooddy of the National Hospital, Queen Square, to be the junior neurologist to serve as secretary for the handling of routine business and day-to-day correspondence with the WFN.

Harvey Cushing Society Sets Deadline for Submission of Titles January 15, 1960, is the deadline for the submission of titles of papers for presentation at the annual meeting of the Harvey Cushing Society to be held in San Francisco (April 14-16, 1960). Eugene Stern is Chairman of the Program Committee, with Kenneth E. Livingston and Robert H. Pudenz serving as members. Members wishing to present exhibits at the 1960 meeting should contact the Secretary of the Society by November 15, 1959....The present officers of the Harvey Cushing Society are James L. Poppen, President; J. Grafton Love, President-Elect; Francis Murphey, Vice-President; Louise Eisenhardt, Historian; Eben Alexander, Jr., Treasurer; and Hendrik J. Svien, Secretary, 200 First Street, S.W., Rochester, Minn.

Geomedical Conference Held in Copenhagen In the "Domus Medica" in Copenhagen, an international geomedical conference (June 20-21, 1959) was held under the chairmanship of Leonard T. Kurland (Bethesda). The conference was sponsored by the World Federation of Neurology, the National Institute of Neurological Diseases and Blindness, and the Danish Multiple Sclerosis Society. The conferees[1] were welcomed by Dr. Frandsen, the Director General of the National Health Service of Denmark, which was followed by dissertations on the history of the organization of the World Federation of Neurology by President Ludo van Bogaert and Executive Medical Officer, Charles M. Poser. The remainder of the program was devoted to a symposium on multiple sclerosis epidemiologic research; to discussions on geomedical methodology and of proposed research in this field; to a consideration of the function of the WFN and its support of comparative epidemiologic research and the formation of a WFN problem commission on biometry and genetics. During the discussions it was proposed that a commission on biometry and genetics be formed with Dr. Kurland as Chairman and this commission be authorized to initiate and stimulate appropriate research effort in this field under WFN auspices....The proceedings of the Copenhagen conference will be published as a supplement in the Acta Scandinavia Neurologia and Psychiatria, of which Dr. Torben Fog is editor.

Masland Becomes New NINDB Director Surgeon General Leroy E. Burney of the U. S. Public Health Service has announced (September 2, 1959) the appointment of Richard L. Masland as Director of the National Institute of Neurological Diseases and Blindness, succeeding Pearce Bailey, the former Director who formulated, developed, and directed the Institute's program since its activation in 1951. This shift in NINDB direction resulted from Dr. Bailey's request to be relieved of his duties as Institute Director in order to take charge of

[1]The conferees present were: Kurland (U.S.A.); Hyllested (Denmark); Allison (North Ireland); Westlund (Norway); Stevenson (England); Miller (England); Poser (U.S.A.); Refsum (Norway); Kurotwa (Japan); Dean (South Africa); Behrend (Germany); and Hall (Switzerland).

NINDB's new International Neurologic Research Programs.... Dr. Masland, who has served as Assistant Director at NINDB for the past two years, has, among other achievements, developed the Institute's extensive collaborative research study pertaining to the neurologic disorders of the newborn, in which 16 hospitals throughout the nation are collaborating. Before coming to NINDB, he was Professor and Head of the Department of Neurology at the Bowman Gray School of Medicine, Research Director of the National Association for Retarded Children, and Director of the Department of Physiology of the U. S. Army's School of Aviation Medicine.... In his new post, Dr. Bailey will encourage the international exchange and coordination of neurologic research and training activities throughout the world. He will serve in a liaison capacity with the World Federation of Neurology, having his headquarters at the WFN Secretariat, Institut Bunge, 59 rue Philippe Williot, Antwerp, Belgium. He will also serve as an advisor to the National Institutes of Health on international neurologic activities overseas.

UCP Advisory Group To Meet in San Juan Brewster S. Miller, Director of Research, United Cerebral Palsy, announces that the next fall meeting of the UCP Research Advisory Committee, Seymour S. Kety, Chairman, will be held in San Juan, Puerto Rico (November 5-8, 1959). The Committee's executive sessions will be held at the Caribe Hilton Hotel, the scientific sessions in the NINDB Laboratory of Perinatal Physiology at the University of Puerto Rico School of Medicine. Reports will be given on recent investigations on the perinatal physiology of primates by Drs. W. F. Windle and C. Murphy Combs of the National Institute of Neurological Diseases and Blindness and by Dr. Joan Mott, a Visiting Scientist and one of the physiologists with Professor Geoffrey Dawes and his group of the Nuffield Institute for Medical Research of Oxford, England. The program also includes a visit to the NINDB Monkey Colony on the Puerto Rican north shore island, Cayo Santiago. Members of the UCP Research Advisory Committee are invited to remain for a small symposium on perinatal physiology, to be conducted by William F. Windle and other outstanding scientists, beginning Monday, November 9....The annual 1959 meeting of United Cerebral Palsy will be held in Miami (Novmber 19-21, 1959).

Here and There Curt Paul Richter, Professor of Psychobiology at the Johns Hopkins School of Medicine and Director of the Psychobiological Laboratory at the Phipps Psychiatric Clinic in Baltimore, will give the thirty-seventh series of Thomas William Salmon Lectures at the New York Academy of Medicine, December 2, 1959. His subject: "Biological Clocks in Medicine and Psychiatry." ...The Eleventh Western Institute on Epilepsy was held in the

Kaiser-Knickerbocker Hotel, Milwaukee, September 10-12, 1959. The meeting was sponsored by the Western Institute on Epilepsy (Mrs. Fred S. Markham, President), the Variety Club of Wisconsin, the Mount Sinai Hospital in Milwaukee, and the Wisconsin Epilepsy League. The chairmen of the scientific program were Jean P. Davis and Edward Schwade; the banquet speech was given by William G. Lennox....The Congress of German Neurologists, featuring circulatory disorders of the central nervous system, took place in Cologne (September 14-16, 1959)....The Eighth World Congress of the International Society for the Welfare of Cripples will be held in New York (August 28-September 2, 1960). The National Society for Crippled Children and Adults will serve as host society for the congress. President Eisenhower has consented to serve as Honorary President, and Dr. Howard A. Rusk will act as President of the Congress....Recent new members of the World Federation of Neurology are Iceland, Nigeria, and Costa Rica....Professor Henri Gastaut of Marseille announces the availability of a series of reprints on various aspects of the epilepsies, published by himself and his collaborators from 1950 to 1958. For a list of these reprints, communications should be sent to the Laboratoire de Neurophysiologie Clinique, 38, boulevard Longchamp, Marseille 1er....Announcements of the deaths of the following neurologists have been made: Professor Oskar Vogt (July 31, 1959), in his 90th year, former Director of the Kaiser Wilhelm Institute of Brain Research in Berlin, Buch; the distinguished Professor Doctor Max Nonne (AAN Honorary-Corresponding Member), Emeritus at the University of Hamburg, August 12, 1959, in his 99th year; and Academy member, Dr. Aaron Bell of New York, August 28, 1959, in his 56th year.... The sixth annual scientific session of the American Association of Electromyography and Electrodiagnosis was held at the Mayo Clinic, Rochester, Minn., on Saturday and Sunday, August 29 and 30, 1959.

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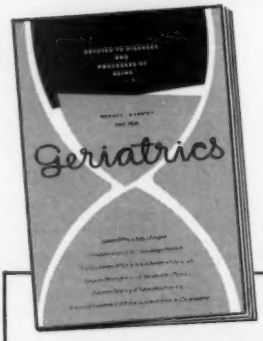

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